



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 43

Alan R. Katritzky

Advances in

Heterocyclic Chemistry

Volume 43

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Advances in

HETEROCYCLIC CHEMISTRY

Edited by

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Preface

Volume 43 of *Advances in Heterocyclic Chemistry* is composed of six chapters by an international set of authors. David Hewitt (Australia) provides us with the first available comprehensive review of heterocyclic six-membered rings containing phosphorus and nitrogen as heteroatoms: the azophosphorins.

Chapters 2 and 3, both authored by Wilhelm Flitsch (Federal Republic of Germany), deal, respectively, with the chemistry of the azaazulenes (not previously covered since 1958) and of hydrogenated porphyrins, a class of increasing importance in biochemical processes. The reactivity of ring-nitrogen atoms in azines toward electrophiles is covered by M. R. Grimmett (New Zealand) and B. R. T. Keene (England) in Chapter 4.

The longest chapter of this volume, authored by Roger Gallo and Christian Roussel (France) and Ulf Berg (Sweden), gives a comprehensive account of the quantitative treatment of steric effects in heteroaromatic compounds—a subject that has been advanced significantly by these authors. Finally, V. N. Charushin and O. N. Chupakhin (USSR) and H. C. van der Plas (The Netherlands) review reactions of azines with bifunctional nucleophiles.

A. R. KATRITZKY

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The Chemistry of Azaphosphorines

DAVID HEWITT

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Chisholm Institute of Technology,
Caulfield East, Victoria, Australia*

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I. Introduction

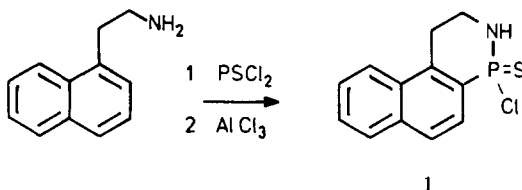
This article concentrates on six-membered heterocycles containing only phosphorus and nitrogen as heteroatoms. Only those compounds containing at least one P—C bond are considered. These heterocycles are not widely discussed in the chemical literature and to date only one short general summary (79MI1) and a review up to 1977 of dihydrophenophosphazines (77RCR855) have been published. The clear impression gained on reviewing the literature of these compounds is that some limited areas have been covered fairly thoroughly by one or two groups, but there has been no systematic study of phosphorus–nitrogen heterocycles and many new areas remain totally unexplored.

Throughout the text compounds are named as derivatives of azaphosphorine. The fully hydrogenated derivatives are named as azaphosphorinanes. This system is followed by Chemical Abstracts. However, there has been recommendation that the unsaturated compounds be named as derivatives of azaphosphinine and the saturated compounds as derivatives of azaphosphinane (83PAC409). Readers are advised that some journals (for example, the *Australian Journal of Chemistry*) now use this system.

II. Compounds with One Phosphorus Atom

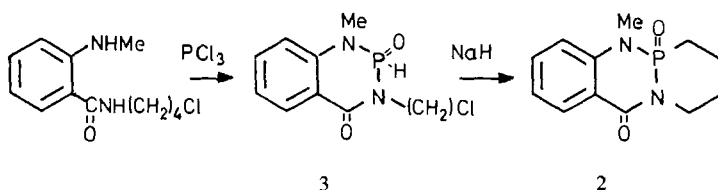
A. COMPOUNDS WITH ONE NITROGEN ATOM

1. 1,2-Azaphosphorines

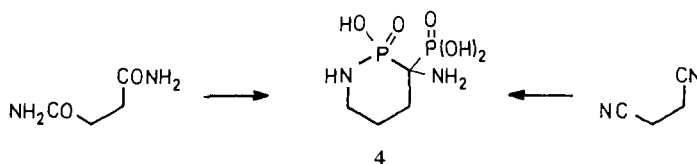


There have been no reports of dibenzo-1,2-azaphosphorines since Edmundson's review (79MI1). However, the naphthalene derivative (1) has been described but its further reactions were not detailed (80IJC(B)404). The tricycle (2) was prepared in low yield by sodium hydride induced cyclization of (3) (79JHC897).

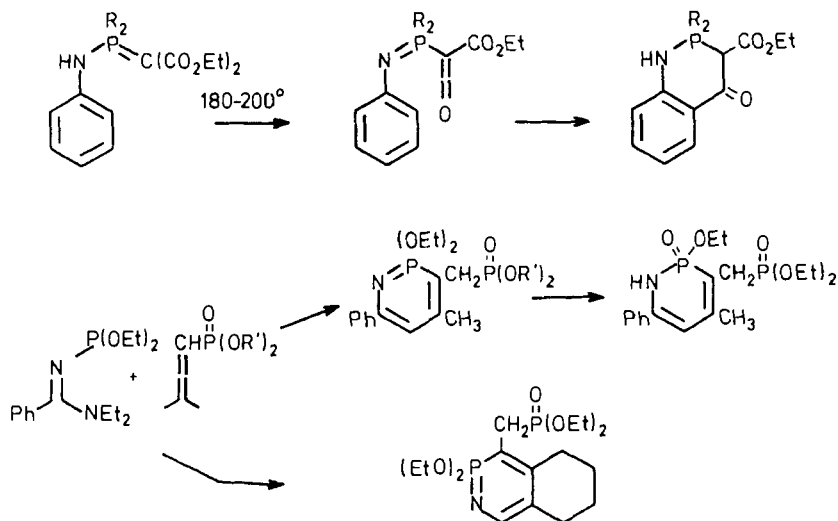
There has been more work on monocyclic systems and a number of patents have been taken out on the amino-diacid 4 (75GEP2343147, 75GEP2343195, 75GEP2417534; 76GEP2456667). Uses proposed for the compound include detergent builder, hardening retardant for gypsum, reduction of calcification



of blood vessels, and additive for toothpastes. These applications are all related to the fact that **4** is an efficient complexing agent for calcium ions.

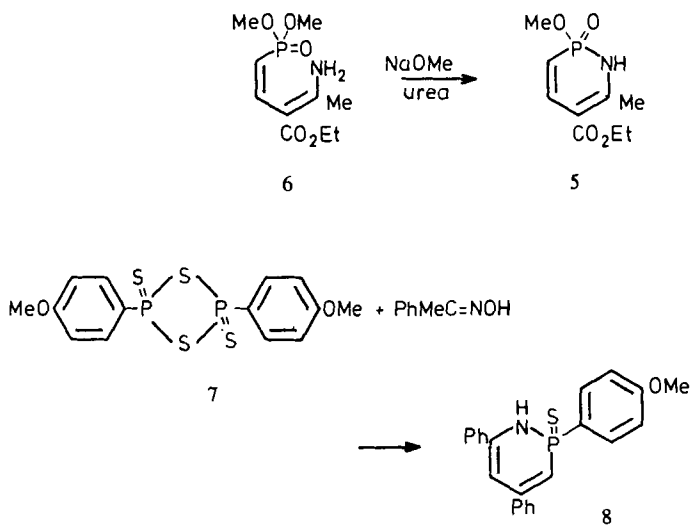


Workers in the Soviet Union have prepared a number of interesting compounds through reactions involving ketene and allene intermediates (79ZOB1004; 82URP888498, 82ZOB789). These reactions have not been exploited by others, but the highly functionalized molecules offer some intriguing synthetic possibilities.

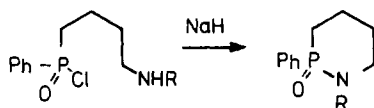


A similar compound (**5**) was prepared by cyclization of the aminophosphonate **6** (78ZOB51). Unfortunately, the source of the starting material was

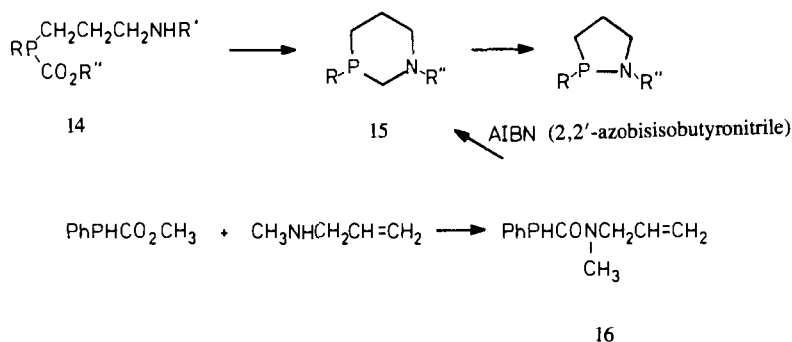
not indicated and there was no discussion of the properties of the product. A further cyclic phosphamide (8) was prepared in the unusual condensation of Lawesson's reagent (7) with acetophenone oxime. The product was formed from a mixture of the two reagents in boiling benzene (84MI1).



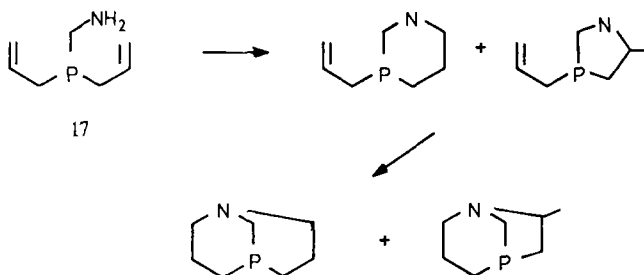
In our laboratories we have been interested in the synthesis of phosphorus-containing analogues of the alkaloid anabasine (77AJC579; 84AJC1631). [A parallel study on nicotine analogues has been pursued by Swan's group (74AJC1759).] We have developed some simple and effective syntheses for a number of 1,2-azaphosphorinanes (**9**, **10**, **11**). Attempts to effect Grignard reactions on either the phosphonate **9** or the amide **11** were unsuccessful. Compound **9** was not substituted on phosphorus by phenylmagnesium bromide or by 3-lithiopyridine. In the latter case, 3-ethylpyridine was isolated. The failure of attack on phosphorus may be due to the constraints imposed by pseudorotation about a phosphorus atom in a six-membered ring. The amide **11**, on the other hand, was easily attacked on phosphorus by phenyllithium or phenylmagnesium bromide. However, only mixtures of ring-opened products were obtained. Some of the cyclic compounds showed weak insecticidal activity.



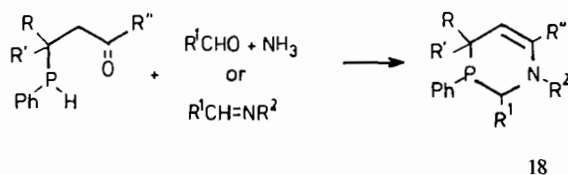
Edmundson (79M11) mentioned the formation of 1,3-azaphosphorinanes in the reaction of aldehydes and ketones with 3-aminopropylphosphines (68CB4032; 73JPR526). Since then, there have been other reports extending the method to the use of carbon disulfide (78JPR600) in place of a carbonyl compound, and for the preparation of benzoazaphosphorines **12** (74M12; 83AJC2095). Another slight modification involved cyclization of the phosphine carboxylic ester **14** (82ZN(B)965). The ester (**14**) was prepared by free radical addition of a phosphine to an allylamine, a procedure used by Isslieb and coworkers (68CB4032) for the preparation of aminophosphines **13**. The product (**15**) was also available when the steps were conducted in the reverse order, that is by free radical cyclization of the acyclic amide **16**.



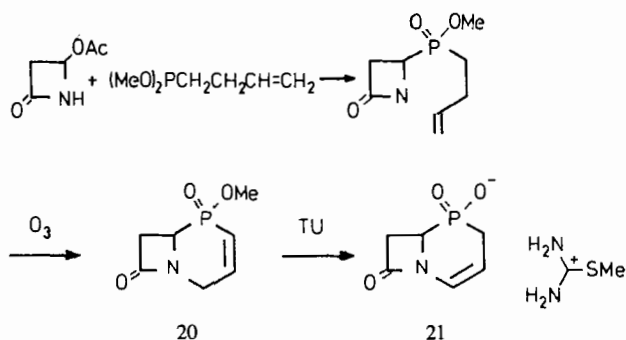
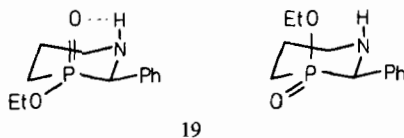
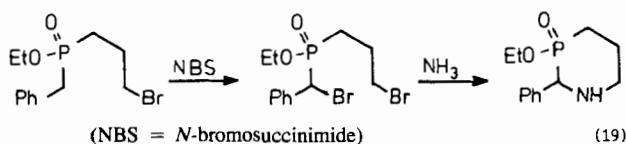
Free radical cyclization of the allylphosphine **17** gave some 1,3-azaphosphorinanes in admixture with other products (83PS73).



A different approach involved treating (3-oxoalkyl)phenylphosphines with aldehydes and ammonia to give **18**. The same phosphorus compounds also reacted with aldimines to give tetrahydro-1,3-azaphosphorines (73M12).



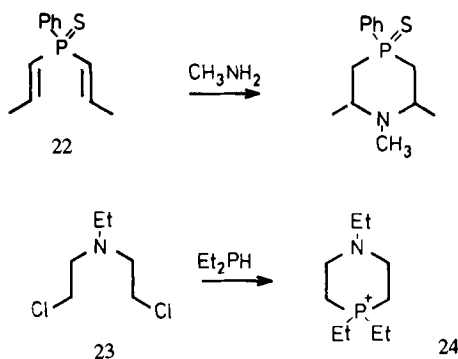
Two groups have deliberately set out to engineer biologically active 1,3-diazaphosphorinanes. In the first, directed to potential insecticides, final ring closure involved the formation of the two C—N bonds (84AJC205). Infrared analysis of the product (**19**) gave evidence for the presence of both stereoisomers about phosphorus. The other group (84CC200) was able to assemble a tetrahydro-1,3-azaphosphorine onto an azetidinone to produce the cephalosporin analogues **20** and **21**. Nuclear magnetic resonance (NMR) spectroscopy at 400 MHz showed an interesting, opposite preference for the position of the double bond in the two compounds.



1,3-Azaphosphorinanes with substituents on nitrogen and phosphorus feature in a British patent concerning the catalytic oxo synthesis of aldehydes and alcohols (72BRP1273042).

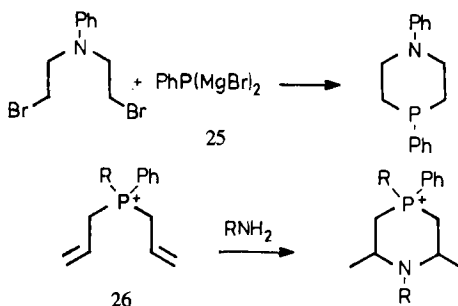
3. 1,4-Azaphosphorines

a. *Monocyclic Systems.* i. *1,4-Azaphosphorinanes.* 1,4-Azaphosphorines are much better known than 1,2- or 1,3-systems and many syntheses take advantage of the symmetry of 1,4-system—they are usually prepared by addition of an amine to a difunctional phosphine or phosphonium salt. An example of a typical synthesis is the addition of methylamine to the phosphine sulfide (**22**). The literature on these systems up to 1974 has been well summarized by Edmundson (79MI1) and will not be repeated here.



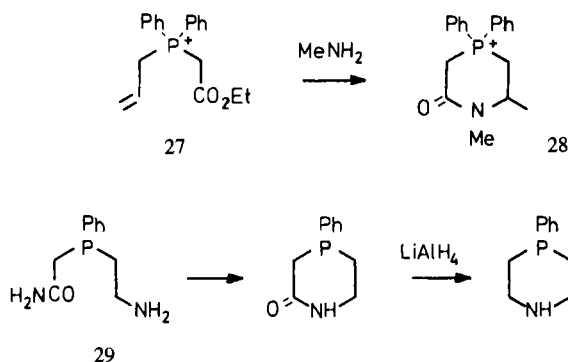
One reference not included by Edmundson demonstrated an inverse addition of a phosphine to a disubstituted amine (**23**) (73IC243). This is a modification of Mann's first synthesis, in which the nucleophile was phenylphosphinedi(magnesium bromide) (**25**) (52JCS3039).

Both the 1,4-azaphosphorinane **24** free base and its hydrochloride form 1:1 blue complexes with cobalt(II) chloride, which gave highly conductive solutions in absolute ethanol. The ^{31}P -NMR peak is at -22.2 ppm, which is typical for a quaternary phosphorus atom (73IC243).

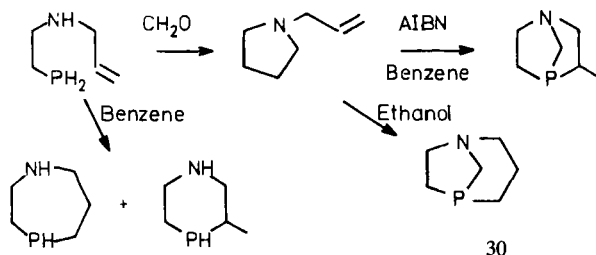


Samaan discusses the ^{13}C -NMR properties of the isomers obtained from the reaction of bisallylphosphonium salt **26** with a number of amines (78CB579). The 1,4-azaphosphoranium salts have the possibility of interaction between the heteroatoms, and this is found in the strong influence of solvent on the ^1H -NMR spectra of the salts. The proton NMR cannot be completely analyzed because of the complex coupling patterns, however, the ^{13}C -NMR spectra are relatively simple. The $^3J_{\text{PC}}$ values between the methyl groups and phosphorus are in the range 11.8–16.2 Hz. About 15 Hz is appropriate for a dihedral angle of 180° . Accordingly, the methyl groups must be axial and antiperiplanar to the phosphorus in a chair-shaped molecule—possibly somewhat flattened at the heteroatom (78CB579).

Most of the 1,4-azaphosphorine derivatives described in the literature have been symmetrical. However, simple modifications in procedure give access to unsymmetrical materials. For example, the alkene ester **27** leads to the cyclic amide **28** (79LA43) and a less-substituted amide is available from the amino amide **29** (70ZC305). In **28**, the ring methyl was shown to be pseudoaxial (antiperiplanar to the C—P bond) by a $^3J_{\text{PC}}$ coupling constant of 16 Hz.

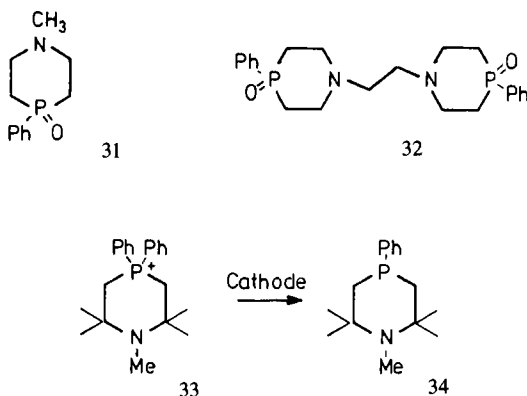


The system is also present in the bicyclic molecules, which are formed by intramolecular free radical addition of a phosphine to an alkene. The particular product formed depends on the solvent used (85M11). Compound **30**

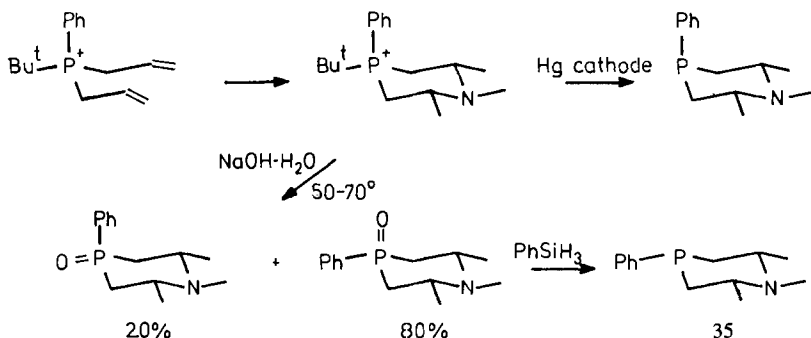


could be converted into the $P=S$ derivative by treatment with sulfur. Methyl iodide reacted on nitrogen to give the quaternary methiodide, and *not* on phosphorus.

Workers in the Soviet Union have made some copper complexes of the mono- (**31**) and dinuclear (**32**) systems (79MI3; 80MI2). X-Ray photoelectron spectra, which give information on inner-electron bridging energies of the ligand W, P, and O and of the Cu and Cl, in this case provided no useful evidence on the nature or position of the bonding.

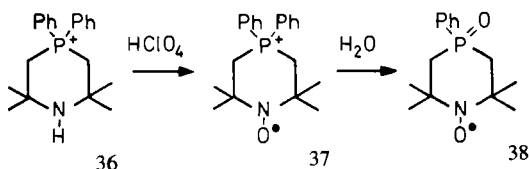


Samaan used reduction at a mercury cathode to convert the phosphonium salt **33** to the phosphine (**34**) (79PS89). This gave the opposite stereoisomer from that available as the major product (**35**) from base hydrolysis followed by silane reduction. The stereochemistry of each compound was established by NMR analysis.

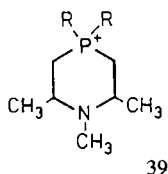


The diphenylphosphonium salt **36** is easily converted by perchlorate oxidation into a stable radical (**37**), which may be hydrolyzed to **38** by base

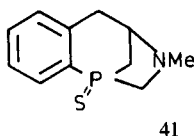
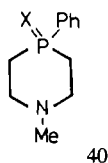
(79TL4833). The radical was characterized by infrared (IR) spectroscopy, electron spin resonance (ESR), and mass spectrometry (MS), and proposed as a possible biological marker. A subsequent X-ray analysis showed **36** and **38** to have chair conformations—somewhat flattened at P in **36** and at N in **38** (83CJC427). In the phosphine oxide **38**, the P=O bond is axial and the P—Ph bond is equatorial.



1,4-Azaphosphoranium salts **39** have been used as phase-transfer catalysts for the Finkelstein and Kolbe reactions (substitution of halogen in alkyl halides by iodide and cyanide, respectively) (78PS145). Representatives of

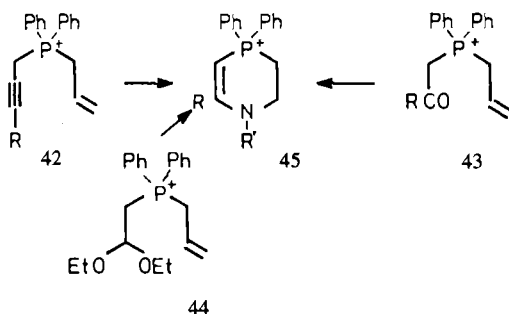


these compounds have been patented for use in vulcanization of elastomeric copolymers of vinylene fluoride (78BEP861672) and as silver ligands in photographic processes (77GEP2651969, 78SZP597627). Others, including **40** (X = O, S), were prepared as isosteric analogues of morphine analgesics, but only the five-membered compound (**41**) was reported as having activity comparable to morphine (76USP3931196). The X-ray crystal structures of **40** (X = S and X = O) show chair conformations with the P—Ph axial, in contrast to the nitroxide **38** (74AX(B)2112).

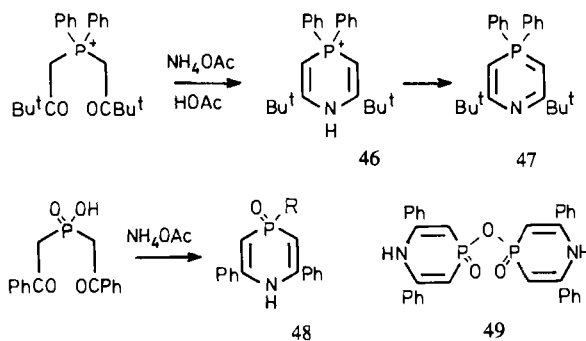


ii. *Tetrahydro-1,4-azaphosphorines*. The most versatile method for the preparation of tetrahydro-1,4-azaphosphorines involves addition of an amine to a suitably disubstituted phosphine, and simultaneous formation

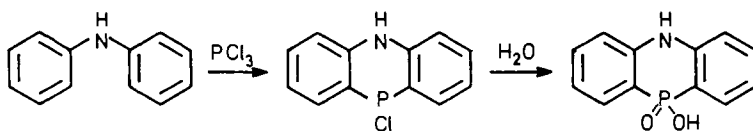
of the two carbon—nitrogen bonds. For example, Samaan used three phosphonium salts (**42**, **43**, **44**) as precursors to compound **45** (79LA43).



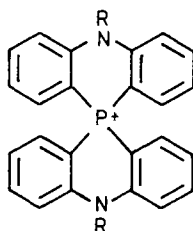
iii. *Dihydro-1,4-azaphosphorines*. Dihydro-1,4-azaphosphorines are generally available by addition of amines or ammonium acetate to alkynyl- or ketomethylphosphines or -phosphonium salts. There have been no new contributions since Edmundson's review (79MI1), except for the production of the di-*t*-butyl compound **46**, which is converted into the aromatic system **47** by ethanolic potassium hydroxide (84PS159), and preparation of the phosphonic acid (**48**, R = OH). The acid (**48**, R = OH) is acylated on nitrogen, and is converted into the 3-bromo- and 3,5-dibromo derivatives by bromine. It may be converted into the acid chloride by thionyl chloride, which in turn gives amides (**48**, R = Et₂N, BuNH, cyclohexylamino, morpholino) and esters (**48**, R = MeO, EtO) and the anhydride (**49**) (81ZOB1481).



b. *5,10-Dihydro-5,10-phenophosphazines*. These compounds have been known since 1890, when Michaelis and Schenk studied the reaction between diphenylamine and phosphorus trichloride in the presence of zinc chloride (1890LA(260)1). The literature up to 1977 has been well summarized



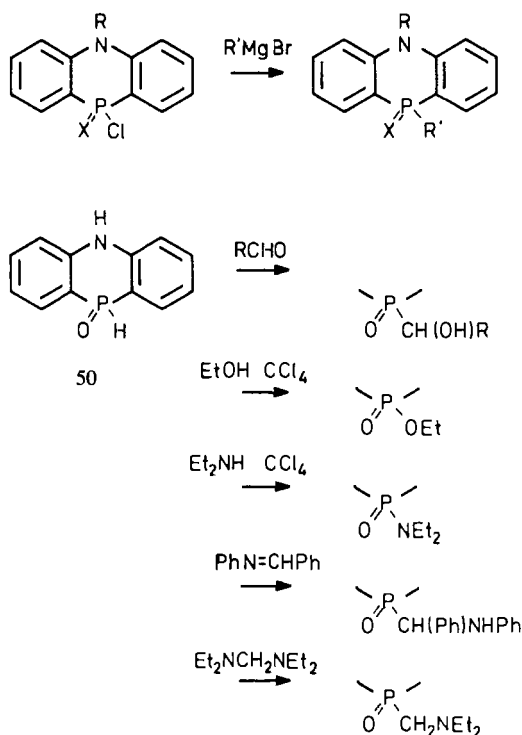
by Bokanov and Stepanov (77RCR855). Not included in their review is Freedman's extensive investigation of the phosphorus trichloride cyclization. They identified the spiro compound as a common side product (71JCS(D)1213; 73MI1). They also analyzed the effect of substituents on the aromatic rings and on the nitrogen atom of the starting diphenylamine (81JOC5373, 81MI1, 81PS269).



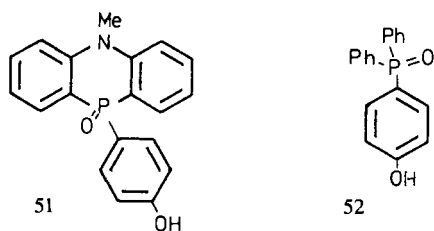
The cyclization failed completely if both rings contained two bromine atoms or if each had a methyl group ortho to the nitrogen. One methyl group in the ortho position was sufficient to prevent formation of a spiro compound. There is no cyclization if the nitrogen is substituted. In a further extension of this work, they included trifluoromethyl substituents (82JOC4637). The presence of these groups on both rings prevented cyclization. With one substituent, cyclization proceeded but no spiro compound was formed. They concluded that the presence of meta-directing groups seriously hinders cyclization.

Most reactions of the phenophosphazine system have already been summarized (77RCR855). The nitrogen atom is easily alkylated by treatment with sodium hydride followed by an alkyl halide (77RCR855; 81ZOB1434). Alkylation on phosphorus is possible via Grignard displacement of halogen (75MI2; 81DIS(B)1891, 81JOC5373, 81ZOB1434; 82ZOB1099), and a number of reactions of the phosphinous acid **50** also lead to P-alkylation (77ZOB579). The second process has the advantage that N-alkylation is not necessary for success. The products find use as antioxidants, polymeric stabilizers, and analytical reagents. Anthelmintic and antitumor activity have also been discussed.

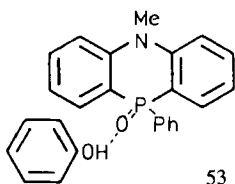
There has been continuing interest in the possibility of interaction between the heteroatoms. Some evidence has been obtained from mass spectroscopy (77RCR855). Since that time an attempt has been made to confirm chemically



the existence of N–P interaction by its effect on the ionization potential of the substituted phenol **51** (78ZOB1316). Transmission of any effect was too inefficient for measurement; the pK_a for **51** was 11.20 compared with 11.11 for **52**. However, for cases in which the phosphorus atom is the reaction center, the effect is claimed to be measurable.



X-Ray crystallography shows these molecules to be nonplanar with a boat-shaped central ring. The dihedral angle between the rings is about 142 – 145° in both phosphines and phosphine oxides (79MI2; 82MI1). The phenol complex **53** has an angle of 149° (79MI4).

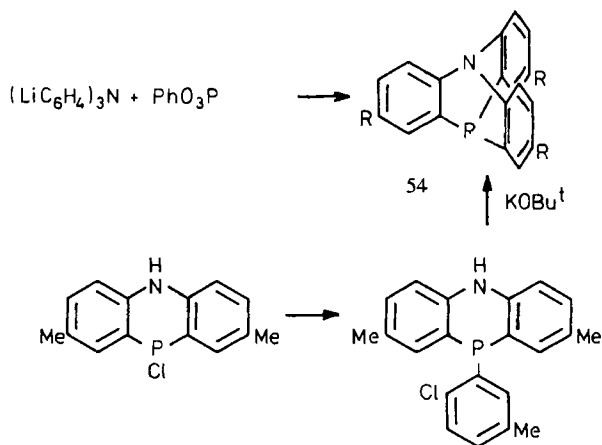


53

Polarographic reduction gives three reduction waves, the first of which is reversible (77ZOB2730). Nitro compounds show four waves, one associated with reduction of the nitro group.

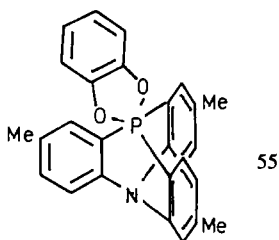
Patents have been taken out covering the reaction of aromatic diamines with phosphorus halide for (1) the preparation of azaphosphazines (66URP189853; 67URP191552); (2) improved hydrolysis of the intermediate acid chloride (81DIS(B)1891); (3) methylation on nitrogen (75MI2); (4) preparation of nitro compounds as potential intermediates for phosphorus-containing azo dyes, fluorescent whitening agents, and photosensitizers (76MI4); (5) preparation of fifteen $P=S$ compounds (79MI5) and eight derivatives used for stabilizers for paraffin oil (70SZP529816); and (6) as oxidation- and wear-inhibiting additives for high-temperature lubricants (67USP3354214).

c. *Triptycenes*. Extension of the common syntheses of phosphazines to the use of trisubstituted aromatic amines as starting materials produces triptycene derivatives (54) (69AG(E)987). The compounds are also available from phenophosphazines in a two-step process, which is claimed to give higher yields (78CB1798).



The ^{31}P -NMR signal in these compounds is at astonishingly high field (+80 ppm from phosphoric acid compared to +7 ppm for triphenylphosphine). Hence the lone pair on phosphorus must have very high s character, leading to C—P—C angles of about 90° . The ultraviolet (UV) spectrum shows little resemblance to azatriptycene (**54**, $\text{P} = \text{N}$). Methylation occurs on phosphorus, and the quaternary phosphonium iodide has a ^{31}P -NMR signal at 4.75 ppm, which confirms the high s character. Bromine converts the phosphine into a phosphine oxide.

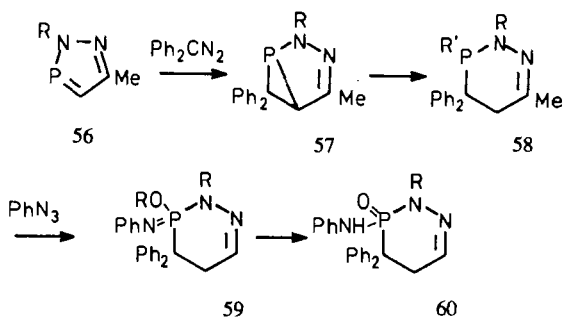
X-Ray crystallography confirmed the NMR data and showed a C—P—C angle of 93.5° (compared with azatriptycene, which has a CNC angle of 97°) (76AX(B)1021). Calculations on the structure using a simplified force field model suggested the same P—C—P angle (93.5°) as found in the X-ray analysis.



These cyclic phosphines react on phosphorus with o -quinones to yield spiroketals (e.g., **55**). X-Ray crystallography showed the phosphorus to have a trigonal bipyramidal configuration. Solution NMR, however, showed only one methyl signal, suggesting rapid intramolecular positional interchange, even at -70° . The mechanism of exchange could be either turnstile or Berry pseudorotation, but no distinction between these was possible (80CB1406).

B. COMPOUNDS WITH TWO NITROGEN ATOMS

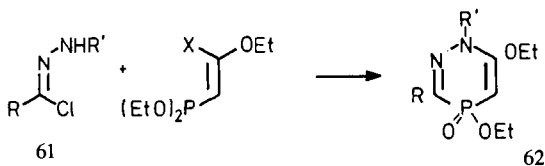
1. 1,2-Diaza-3-phosphorines



Arbuzov and colleagues studied the ring expansion of the diazaphospholes (**56**) (82IZV2730). Reaction with diphenyldiazomethane gave the bicyclic intermediate **57**, which could be converted into the diazaphosphorine **58** ($R = \text{Ph, Ac}$; $R' = \text{Cl, MeO, EtO}$) by treatment with either hydrochloric acid or an alcohol. The phosphine (**58**, $R = \text{Ph}$; $R' = \text{OMe}$) could be converted into the corresponding sulfide, whose conformation was determined by NMR spectroscopy (82IZV2730). It was found to be a half-chair with a pseudo-equatorial $\text{P}=\text{S}$ bond. The precursor phosphine has a similar conformation, with the phosphorus lone pair in the pseudoequatorial orientation. The latter compound was found to have the same conformation in the solid state by X-ray crystallography (78DOK358). The phosphine was quantitatively converted into **59** by the Staudinger reaction with phenyl azide (83IZV418). This product reacted with methanol to give the phosphoramidate **60** (82IZV2723). Crystal structures were measured for **59** and **60**. They were found to be distorted boats with $\text{N}^2\text{N}^1\text{C}^6\text{C}^5$ approximately planar and P^3 and C^4 out of plane on the same side. $\text{N}-\text{Ph}$, $\text{C}-\text{Me}$, and $\text{P}=\text{NPh}$ were all equatorial and $\text{O}-\text{Me}$ was axial. The $\text{P}=\text{N}$ bond in **59** is somewhat shorter than usual. In contrast, the $\text{P}=\text{O}$ bond in **60** is equatorial and a little longer than normal.

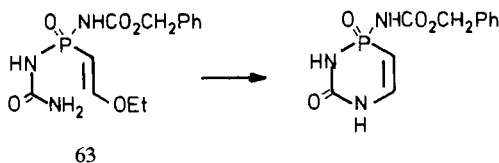
2. 1,2-Diaza-4-phosphorines

There is only one report of the preparation of this ring system. It was achieved by cyclization of hydrazones **61** with phosphites. Ten different compounds (**62**, $R = \text{Ph, Ac, CO}_2\text{Et, Bz, O}_2\text{NPh}$; $R' = \text{Ph, } p\text{-BrPh, } p\text{-tolyl}$) were prepared in yields of 63–93% (82ZOB2172).

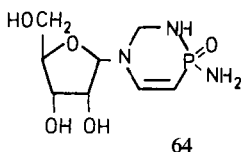


3. 1,3-Diaza-4-phosphorines

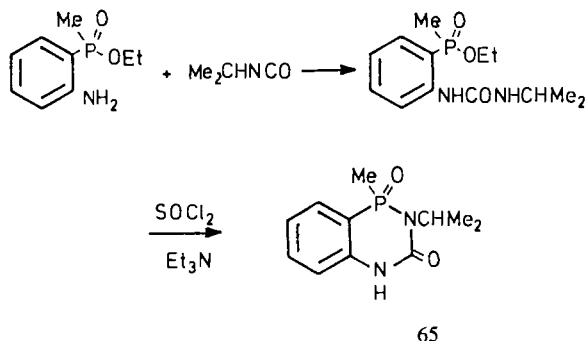
This ring system has been entered by cyclization of the phosphorus-containing urea enol ether **63** (78MI1). These compounds have been used in



the synthesis of nucleotide analogues (e.g., **64**), which represent transition state models for the enzyme *Escherichia coli* cytidine deaminase. The models are potent slow-binding inhibitors that bind reversibly with no covalent linkage (82BBR1467; 84JBC1361).



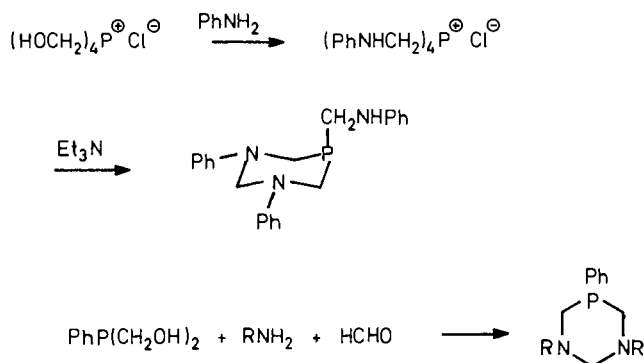
There is one report of the preparation, also from substituted ureas, of benzo-fused compounds (**65**), which were patented for use as herbicides. No data on herbicidal activity were presented (84USP4433149).



4. 1,3-Diaza-5-phosphorines

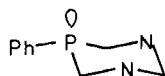
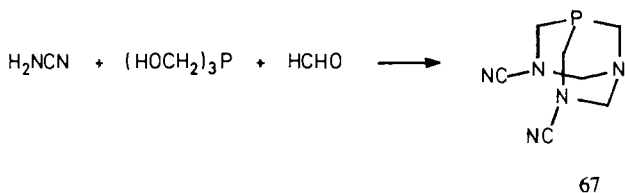
a. *Monocyclic Systems.* These compounds are probably best considered in their reactions as masked aldehydes and should be compared with trioxane or tetramethylenehexamine. They have been studied almost exclusively in connection with their use as flame retardants for cotton fabrics (73USP367971, 73USP374584). The monocyclic compounds have nearly always been prepared by reaction of tetrakis(hydroxymethyl)phosphonium chloride or tris(hydroxymethyl)phosphine with amines (72JOC2752; 74USP529974, 74USP529975; 76USP3954866).

A minor modification used the phosphine **66** in the presence of an amine and formaldehyde (79IZV2771; 80IZV2129; 81TL229). The mechanism has been studied by Arbuzov and colleagues (80IZV1438, 80IZV2129), who also reported exchange of substituents on nitrogen by reaction with amines (80IZV2417).

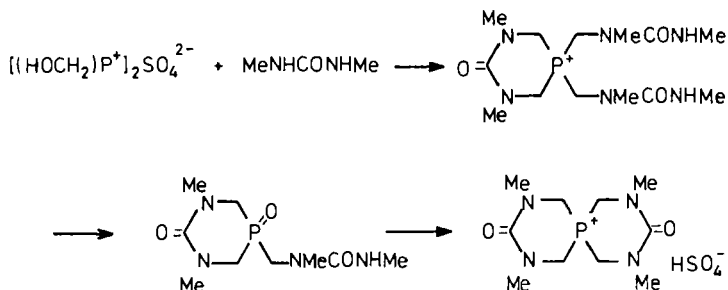


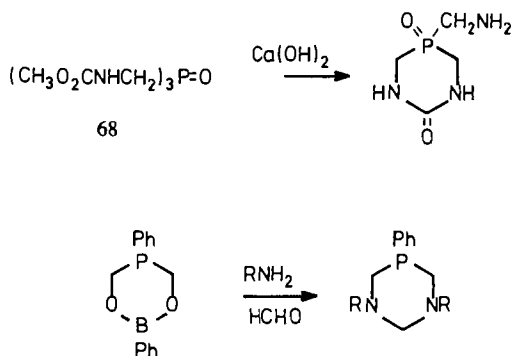
66

The two nitrogen atoms may be simultaneously derived from urea or cyanamide as indicated in the following examples (72JHC715, 72JHC1295; 73USP374584; 81PS147). The bicyclic product **67** is reported to explode on rapid heating.



The second series of reactions using *N,N'*-dimethylurea was studied in an effort to understand the mechanism of fabric flame-proofing (81PS207). Under some conditions these reactions can produce polymers that may be used as flame-retardant finishes for cotton.

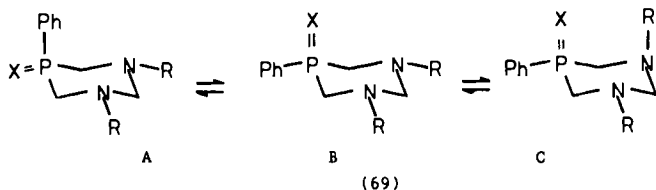




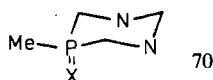
A unique entry to the ring system is via base-catalyzed cyclization of the phosphine oxide **68** (81USP212298). There is one example of synthesis by heteroatom exchange of a cyclic boron compound (80IZV952). The reactions and chemical properties have not been extensively discussed. However, reaction with electrophiles occurs preferentially on phosphorus. Accordingly, alkylation with alkyl halides leads to phosphonium salts, and oxidation gives the phosphorus oxide (72JHC715; 83IZV1379). The corresponding results are observed for the bicyclic derivative **67** (73USP374584).

Arbuzov's group showed by NMR analysis the presence of a chair conformation with P—Ph equatorial and the nitrogen lone pair axial. Use of Ni(acac)₂ (acac = acetylacetonate) simplified the spectra by decoupling hydrogen and phosphorus. At low concentrations, coordination of the nickel is with phosphorus (80IZV1571).

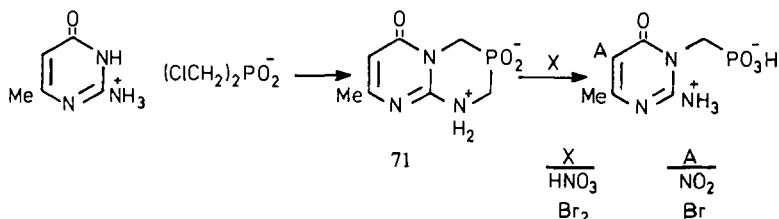
The same group (80IZV721; 81IZV1539; 82IZV127) used dipole moments to study the contributions of different conformers for various P=X compounds (**69** A–C). These have been investigated for the cases where X = electron pair, O, S, and Se. As the coordination number of the phosphorus atom increases, there is an increasing axial orientation of the phenyl on phosphorus. Configuration C is disfavored when R = benzyl and X = O or S.



There have also been some molecular orbital (MO) calculations using CNDO/2, which were confirmed by NMR studies (85IZV1296). For **70**, when X = S, the methyl group is equatorial and the NH bonds are axial.

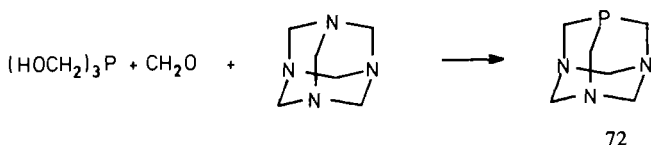


There is one literature report of a much more complex structure containing the 1,3,5-diazaphosphorine ring system (70IZV2254). Compound **71** was prepared during the course of a synthesis of nucleotide analogues containing a C—P bond in the *N*-alkyl chain.



Ishizu has reported on the toxicity towards mice of these compounds and their acyclic precursors (75MI1). They appear to be somewhat less toxic than other phosphorus-containing flame retardants.

b. *Adamantane Types*. Reaction of tris(hydroxymethyl)phosphine or tetrakis(hydroxymethyl)phosphonium salts with hexamethylenetetramine in the presence of formaldehyde gives 1,3,5-triaza-7-phosphaadamantane (**72**, sometimes referred to as monophosphaurotropin)(73USP391189; 74JHC407; 75JHC579) in moderate yield. Fluck produced **72** by reaction of the phosphine with paraformaldehyde and ammonium acetate (75CZ246).

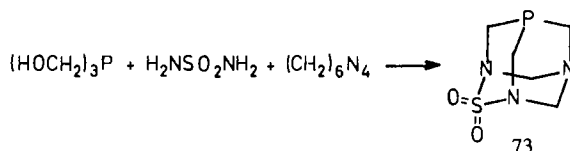


Both the phosphine (**72**) and its *P*-oxide are preferentially acylated (77JHC337) on nitrogen and alkylated on nitrogen by alkyl halides (73USP391189; 74JHC407; 75CZ246, 75JHC579; 77ZN(B)499; 81PS255) and by formaldehyde (76MI3). This is in contrast to the normal situation where phosphorus quaternizes first (52JCS3039). The *N*-benzylammonium chloride is stable on heating—there is no migration of the benzyl group to phosphorus (75CZ246). Oxidation and sulfonation occur on phosphorus, and this has been confirmed by X-ray analysis (78PS199). UV photoelectron spectroscopy shows only one low-energy peak, consistent with large nitrogen–phosphorus interaction (82IC543).

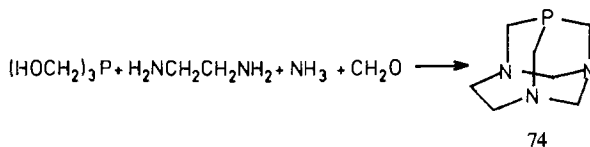
The cage compound **72** forms air-stable, crystalline solids with excess $M(CO)_6$ ($M = Cr, Mo, W$) or $Fe(CO)_5$ in refluxing dry diglyme (75IC1217; 76IC816). A complex containing two phosphaadamantane ligands and a Cu—Cu bond is formed when the adamantane (**72**) is treated with copper(II) chloride in 2,2-dimethoxypropane (80MI1). Infrared and NMR spectra suggest that the metal is bonded to phosphorus.

The *P*-methylphosphonium derivative has been made by cyclization of tris(hydroxymethyl)methylphosphonium iodide with ammonium acetate (77CZ304). An incorrect abstract (87CA184600) of this work suggests that direct *P*-methylation is possible. X-Ray, NMR, and IR spectra are reported. [78ZN(B)1257] The X-ray spectra show C—P—C angles of about 102° and Me—P—C angles of 116° .

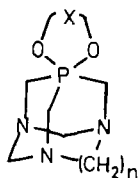
The related sulfone (**73**) is formed in an analogous reaction (74JHC1085). In contrast to **72**, this compound shows the expected higher reactivity at phosphorus than nitrogen. It is alkylated on phosphorus by methyl iodide and converted into the *P*-oxide by *t*-butyl hydroperoxide. This compound was also prepared as a potential flame retardant. The crystal has C—P—C angles of 95.8 , 96.4 , and 98.0° , very little changed from phosphatriazaadamantane (76JHC757).



A ring-expanded analogue (**74**) is available if the hexamethylenetetramine is replaced by a mixture of ammonia and ethane-1,2-diamine (74MI1). This compound is resistant to methylation by methyl iodide on both nitrogen and phosphorus, but is oxidized on phosphorus by *t*-butyl hydroperoxide.

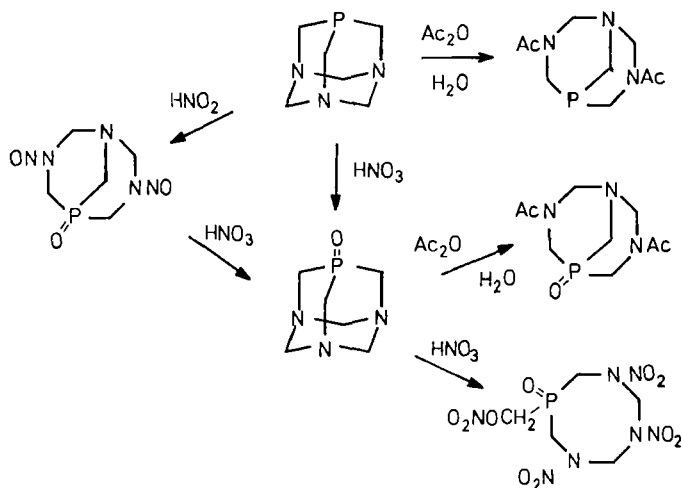


Few other reactions of the triazaphosphaadamantane have been studied. They react with organic azides to give $P=NEt$ and $P=NPh$ derivatives. In general, they react more slowly than acyclic phosphines (82PS105). Reaction with *o*-quinones and related compounds (80TL1449) gives spiroketals (**75**).



75

The ^{31}P -NMR spectra of the spiroketals and their precursors show a strong effect of ring size (^{31}P signal at -89.3 , -102 , -88 , -67.4 for phosphines, and -52.3 , -69.7 , -54 , -39 for spiroketals with $n = 0, 1, 2, 6$, respectively). The different hybridization of phosphorus reflected in these values probably goes some way toward explaining the apparently anomalous relative reactivity of nitrogen and phosphorus in these heterocycles. Nitration and nitrosation produce partially ring-opened potential explosives (77JHC337).

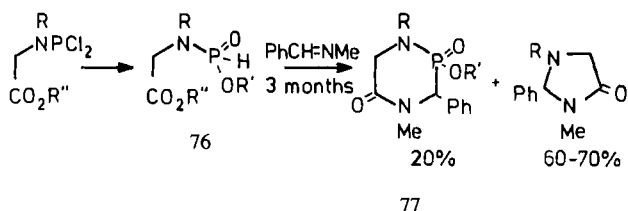


The main interest in these materials is as flame retardants and for improving wrinkle recovery in cotton fabrics. A number of patents have been taken out covering these applications (73USP391189; 75USP614994, 75USP3865618, 75USP3899618; 76USP3932390; 79USP964854). They may also serve as light stabilizers for polypropylene in combination with calcium stearate (77GEP2545292) and as an antioxidant when used as the polypropylene-soluble phenol salts (77GEP2544014). Another patent concerns their use as a cross-linking agent for phenolic novolacs with increased shelf-life prior to injection molding (77USP4056512).

Triazaphosphaadamantane forms complexes with phenol, catechol, resorcinol, and hydroquinone. These compounds are similar to those formed by hexamethylenetetramine, and were proposed as intermediates for the preparation of Bakelite-type resins (76MI1).

5. 1,4-Diaza-2-phosphorines

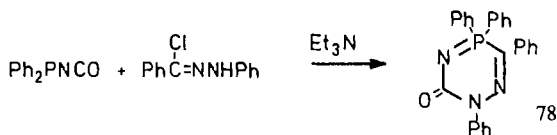
The only reference to this class of compounds involves addition of the phosphinate **76** to *N*-methylbenzaldimine (82ZOB2465). The reaction took place during 3 months and produced **77** in only 20% yield, the major product having lost phosphorus.



C. COMPOUNDS WITH THREE NITROGEN ATOMS

1,2,4-Triaza-5-phosphorines

The reaction of phosphine isocyanates with chlorohydrazones gives triazaphosphorines (**78**) (72ZOB1876). This is representative of a general class of syntheses, in which the $\text{P}-\text{X}=\text{Y}$ or $\text{P}-\text{X}\equiv\text{Y}$ functional group behaves as a 1,3-dipole (68ZOB2819, 70ZOB574; 71AG397, 71ZOB1972, 71ZOB1976).



The other possible classes of compounds containing three nitrogens and one phosphorus atom, 1,2,3-triaza-4-phosphorines, 1,2,3-triaza-5-phosphorines, and 1,2,5-triaza-3-phosphorines, have not been reported.

D. COMPOUNDS WITH FOUR NITROGEN ATOMS

1,2,3,4-Tetraaza-5-phosphorines have not been described.

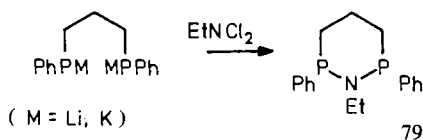
III. Compounds with Two Phosphorus Atoms

A. COMPOUNDS WITH ONE NITROGEN

1-Aza-2,6-diphosphorines

This is the only representative of this class—there have been no reports of 1-aza-2,3-diphosphorine, 1-aza-3,4-diphosphorine, 1-aza-2,4-diphosphorine, 1-aza-3,5-diphosphorine, or 1-aza-2,5-diphosphorine.

Isslieb and Boettcher described a general procedure for the preparation of cyclic molecules containing the P—E—P functionality. The preparation involves reaction of metal phosphides with appropriate electrophiles, such as *N,N*-dichloroethylamine, to give **79** (76MI2).

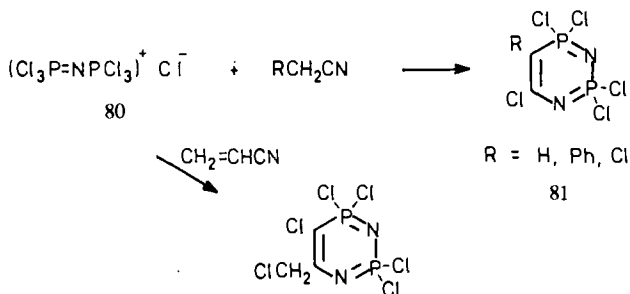


B. COMPOUNDS WITH TWO NITROGENS

No reference was found to 1,2-diaza-3,4-diphosphorine, 1,2-diaza-4,5-diphosphorine, 1,2-diaza-3,5-diphosphorine, 1,2-diaza-3,6-diphosphorine, 1,3-diaza-4,5-diphosphorine, 1,3-diaza-2,5-diphosphorine, or 1,4-diaza-2,6-diphosphorine.

1,3-Diaza-2,4-diphosphorines

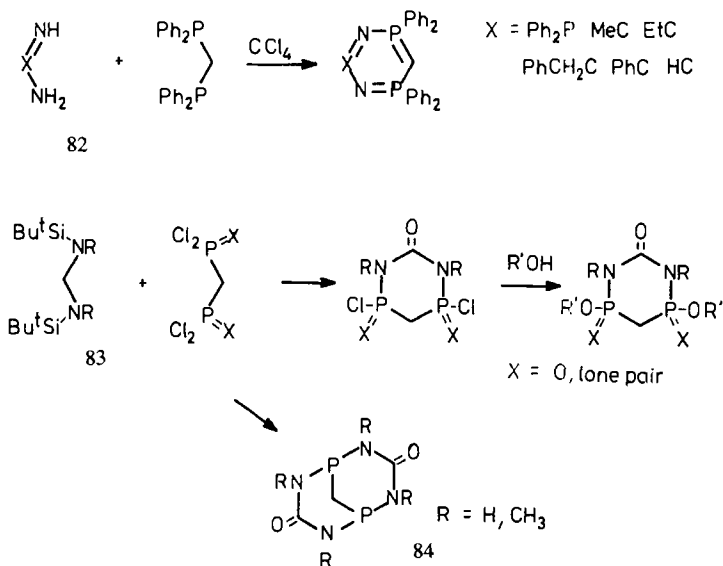
Fluck and co-workers described the reaction of hexachlorodiphosphazonium chloride (**80**) (for which an improved synthesis was developed) with



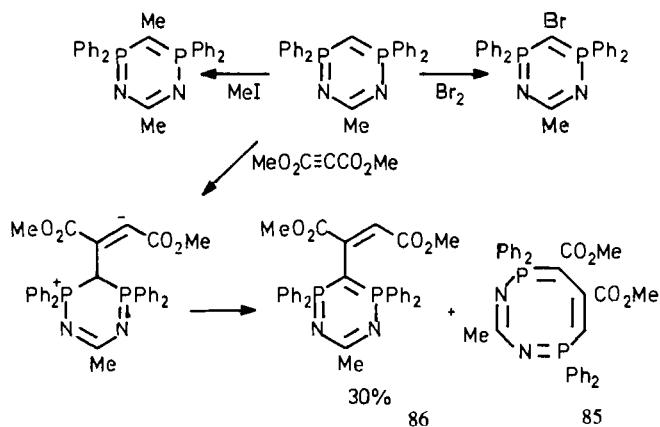
chloroacetonitrile, which forms the highly chlorinated diazadiphosphorine **81** (77MI1, 77MI2, 77PS209). The reaction proceeds less efficiently with acetonitrile and acrylonitrile and leads only to acyclic products with dichloroacetonitrile. The products were characterized by IR, NMR, and MS but their reactions were not extensively investigated.

2. 1,3-Diaza-4,6-diphosphorines

This class has been entered only by combination of methylenediphosphines with bifunctional reagents, such as substituted guanidines (**82**) (72CB2476) and silylated ureas (**83**) (84CZ402). Under some circumstances, the diphosphine may react with a second mole of urea to produce bicyclic products (**84**) (84AP1053).

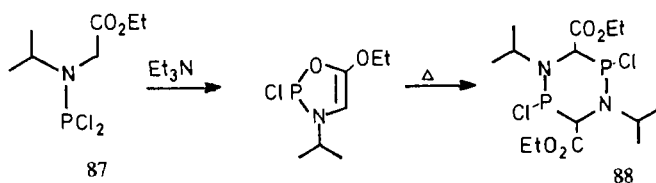


The products derived from guanidines show aromatic reactivity. They are strongly nucleophilic and may be brominated and methylated in the heterocyclic ring. Reaction occurs with dimethylacetylene dicarboxylate to form the eight-membered insertion product **85**. However, this is possibly produced by a two-step process involving electrophilic substitution of the heteroring rather than direct Diels–Alder addition, and this proposal is supported by the simultaneous formation of the substitution product **86**.

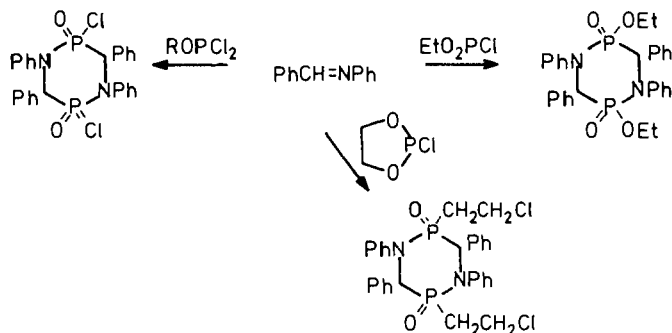


3. 1,4-Diaza-2,5-diphosphorines

Two routes have been used to access this class of compounds. The first is base-catalyzed cyclization of the chlorophosphine ester **87**, which proceeds via a five-membered ring intermediate that may then be thermally cyclized by repeated distillation to form the diazadiphosphorine **88** (77ZOB1422; 78ZOK 739).



The second pathway involves the addition of chlorophosphites to imines. The cyclized products form in 20–35% yield (82ZOB930; 83IZV432). The compounds that have been reported are indicated—no significant chemical reactions have been described.



C. COMPOUNDS WITH THREE NITROGENS

No reports could be found that referred to 1,2,3-triaza-4,5-diphosphorine, 1,2,3-triaza-4,6-diphosphorine, 1,2,4-triaza-3,5-diphosphorine, or 1,2,4-triaza-3,6-diphosphorine.

IV. Compounds with Three Phosphorus Atoms

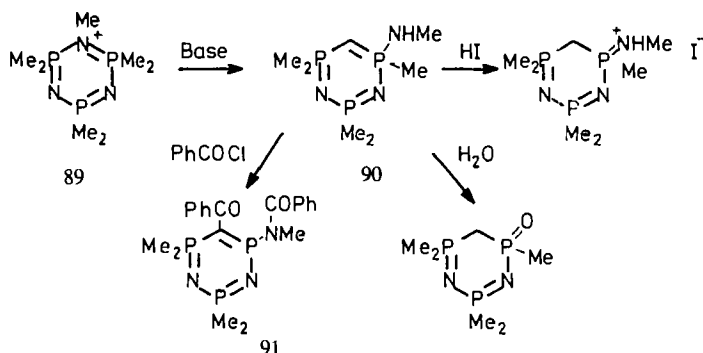
A. COMPOUNDS WITH ONE NITROGEN

No references could be located to any report of 1-aza-2,3,4-triphosphorine, 1-aza-3,4,5-triphosphorine, 1-aza-2,3,5-triphosphorine, 1-aza-2,4,5-triphosphorine, 1-aza-2,3,6-triphosphorine, or 1-aza-2,4,6-triphosphorine.

B. COMPOUNDS WITH TWO NITROGENS

2. 1,3-Diaza-2,4,6-triphosphorines

Oakley's group discovered the base-induced rearrangement of the 1,3,5-triaza-2,4,6-triphosphorine **89** to the 1,3-diaza-2,4,6-triphosphorine **90** (75CC454; 77CJCC3651). X-Ray analysis showed a slightly nonplanar ring with only slight variation in the P—N bond lengths, in marked contrast to the case of P_3N_3 rings (e.g., **89**) (77CJC2534). Unlike the situation for aminophosphazines, the exocyclic P—N bond is easily cleaved by aqueous ethanol. The ring shows aromatic character in that it is insensitive to oxygen, gives no Wittig reaction, but may be acylated on carbon (and nitrogen) by benzoyl chloride to give **91**.



V. Compounds with Four Phosphorus Atoms

Three groups of compounds comprise this class: 1-aza-2,3,4,5-tetraphosphorines, 1-aza-2,3,4,6-tetraphosphorine, and 1-aza-2,3,5,6-tetraphosphorine. No references to any of these could be located.

References

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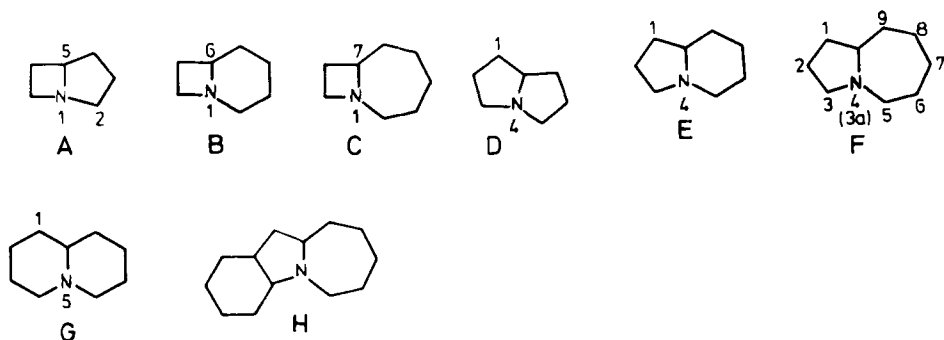
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I. Introduction

A comprehensive review of the entire field of N-bridgehead heterocyclic compounds given by W. L. Mosby covers the literature until 1958 (61MI1). Heterocycles of this type have since found interest in chemistry and



SCHEME 1

biochemistry. The topology of different classes of N-bridgehead bicycles is given in Scheme 1, together with the numbering as proposed by *Ring Index* (84MI6). 4-Azaazulenes (F) have been called 3a-azaanulenes, hitherto assigning position 3a to the bridgehead nitrogen. Here we follow *Ring Index* because it allows for a uniform numbering of all N-bridgehead bicyclic compounds.

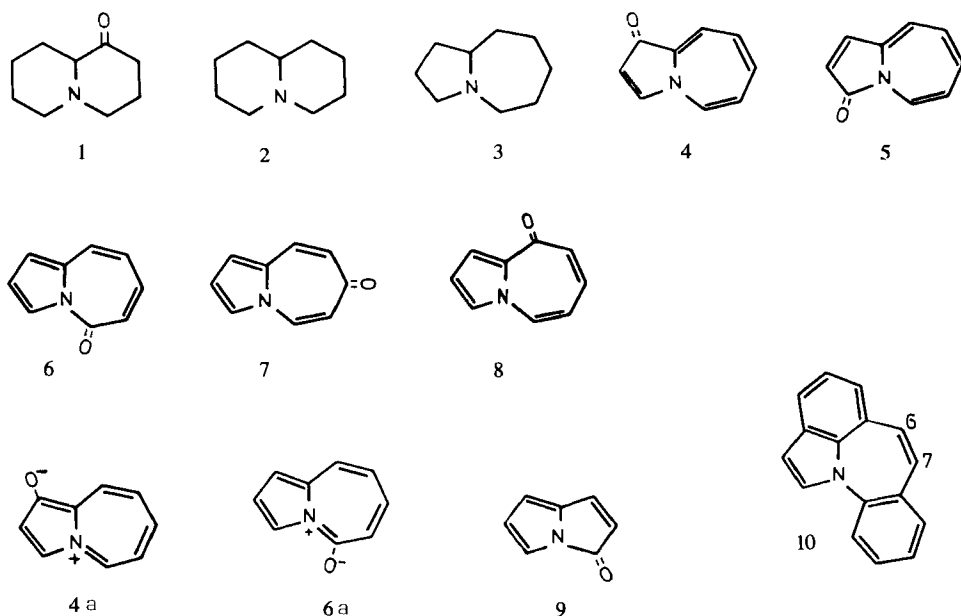
Compounds of type A–C have only rarely been investigated (84MI2). Pyrrolizines D (84AHC(37)1), indolizines E (84MI4), and quinolizines G (84MI3) have been reviewed. Some 4-azaazulene chemistry may be found in a general review on azaazulenes (81H547), and a report on azepino[1,2-*a*]indoles [i.e., 2,3-benzo-4-azaazulenes (H)] has appeared (84HC-1).

The first 4-azaazulene derivative was discovered during investigations of lupine alkaloids. Wolff–Kishner reduction of quinolizin-1-one (1) was shown to give lupinane 2. Clemmensen reduction of 1, however, gave an isomer of 2. Both compounds were regarded as cis–trans isomers, similar to those of decalins. Unconvinced that this kind of isomerism could occur with a bridgehead nitrogen atom, Prelog and Seiwerth proposed the alternative structure 3 for the Clemmensen reduction product, proving this by an independent synthesis (61MI1).

Apart from investigations of the mechanism of the Clemmensen reaction ensuing from the formation of 3, work on the reactivity of nitrenes (Section IV,A,4), as well as studies of photochemical rearrangements of acridine N-oxides (Section IV,B), have led to 4-azaazulenes.

Moreover, the 4-azaazulene skeleton has been found in natural products, such as *Cephalotaxus* alkaloids and *Erythrina* alkaloids (78MI1) (Section V,B).

The 4-azaazulene π -system was first studied by G. Jones (68TL1935). A number of synthetic routes to unsaturated derivatives have been developed and selected derivatives have been used as starting materials for the synthesis of cyclazines (78AHC(22)321; 84 HC-1).



The number of reports on mechanistic investigations, as well as on the synthesis and investigation of natural products and aromatic derivatives, has increased steadily in recent years. Further developments are to be expected, especially in the natural product field.

II. Structure

A. THEORETICAL CHEMISTRY

Topological control of the position of the carbonyl groups on the properties of 4-azaazulenones **4–8** has been studied by self-consistent field (SCF) calculations and a frontier orbital model was proposed based on dipolar structures of oxo derivatives, such as **4a** and **6a** (85MI2, 85UP1).

The influence of electron-donating substituents on the energy of frontier orbitals may be deduced from the eigenvectors of the corresponding orbitals of azulene, as shown in Fig. 1. It follows that donating groups in positions 1 and 3 raise the energy of the highest occupied molecular orbital (HOMO), thus destabilizing the π -system, whereas a stabilization by similar perturbations in positions 5, 7, and 9 originates from an extending HOMO–LUMO (lowest unoccupied molecular orbital) gap brought about by a

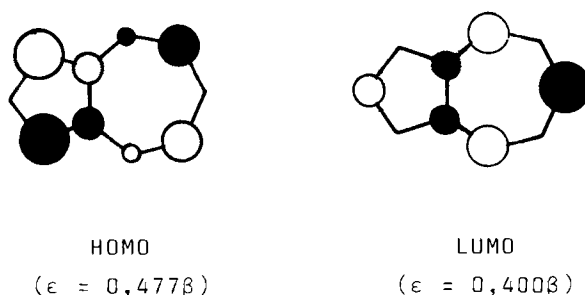


FIG. 1. Frontier orbitals of azulene.

TABLE I
HESS AND SCHAAD RESONANCE ENERGIES (REPE)^a OF 4-AZAAULENES^b

	4	5	6	7	8
REPE	-0.032	-0.007	0.016	0.014	0.012
$\Delta\text{HOMO-LUMO } (\beta)$	0.065	0.064	0.307	0.365	0.373

^a And HOMO-LUMO gaps.^b (83MI1).

destabilization of the LUMO. The model must be revised or qualified for a rationalization of 4-azaazulenones. Resonance energy (REPE) values of 4-azaazulenones are also given in Table I.

The frontier orbitals of 4-azaazulen-5-one (**6**) have been compared with those of pyrrolizin-3-one (**9**) (78CB2407).

B. MOLECULAR SPECTRA

1. NMR Spectra

Protonation of 4-azaazulenones and tautomerism of 4-azaazulenes, which have been studied mainly by ¹H-NMR spectroscopy, are covered in Sections III,B and III,A, respectively.

¹H-NMR spectra have been compared for the only uncharged, fully conjugated 4-azaazulene (**10**) and its 6,7-dihydro derivative. The 6,7-double bond gives rise to a 0.3 to 0.6-ppm high-field shift of the remaining protons (83JHC37).

¹H-NMR spectra of 4-azaazulenones **5–8** are shown in Table II. The average chemical shift (δ) of **5** differs from those of **6–8** by 0.74–0.94 ppm, thus indicating a destabilization of the π -system of **5**, which unlike **6–8** does not

TABLE II
 ^1H -NMR SPECTRA OF 4-AZAAZULENES (5-8) IN CDCl_3

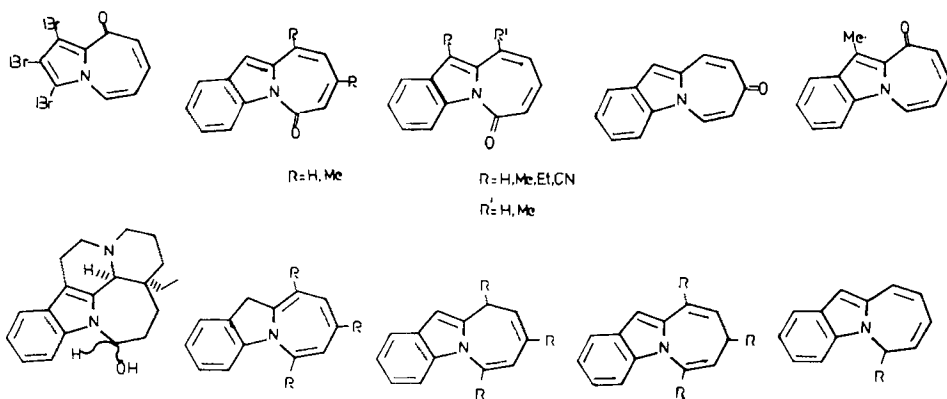
	H-1	H-2	H-3	H-5	H-6	H-7	H-8	H-9	δ	Ref.	$J_{1,2}$	$J_{2,3}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$J_{8,9}$
5	7.02	6.51	—	6.73	4.98	5.72	5.52	5.52	6.01	<i>a</i>	5.5	—	10.1	7.6	11.4	7.7
6	6.79	6.77	8.10	—	6.50	7.00	6.21	7.30	6.95	<i>b</i>	3.8	3.2	—	12.5	8.4	11.2
7	6.72	6.52	7.20	7.39	5.93	—	6.25	7.15	6.74	<i>c</i>	3.8	3.8	10.3	—	—	12.3
8	7.37	6.56	7.20	7.40	5.82	6.72	6.53	—	6.79	<i>d</i>	4.0	2.8	9.6	8.6	12.1	—

^a (86MI1).^b (78CB2407).^c (82JCS(P1)1123).^d (78CB2407).

contain a pyrrole ring. Similar conclusions may be drawn from the 3J values of the seven-membered rings (86MI1).

Chemical shifts of 1,2,3-tribromo-4-azaazulen-9-one (**11**) (69JCS(C)1028) and 1,2-benzo-4-azaazulenones **12** (71JCS(C)3418), **13** (75CPB2818), **14** (71JCS(C)3418), and **15** (68TL1935) (69JCS(C)1028) have been reported.

The relative and predominant conformations of diastereomeric 14-hydroxy-(*E*)-homoeburnanes **16** have been established by ^1H - and ^{13}C -NMR spectroscopy, indicating that previous assignments of C-12 and C-20 signals of *trans*-(*D/E*)-ring fused *vinca* alkaloids must be reversed (85JCS(P2)1319).



2. Other Spectra

Infrared (IR) carbonyl frequencies of 4-azaazulenones **6** and **8**, pyrrolizin-3-one (**9**), and partially hydrogenated derivatives have been discussed in terms of π -interactions and ring size (61JOC4712; 78CB2407).

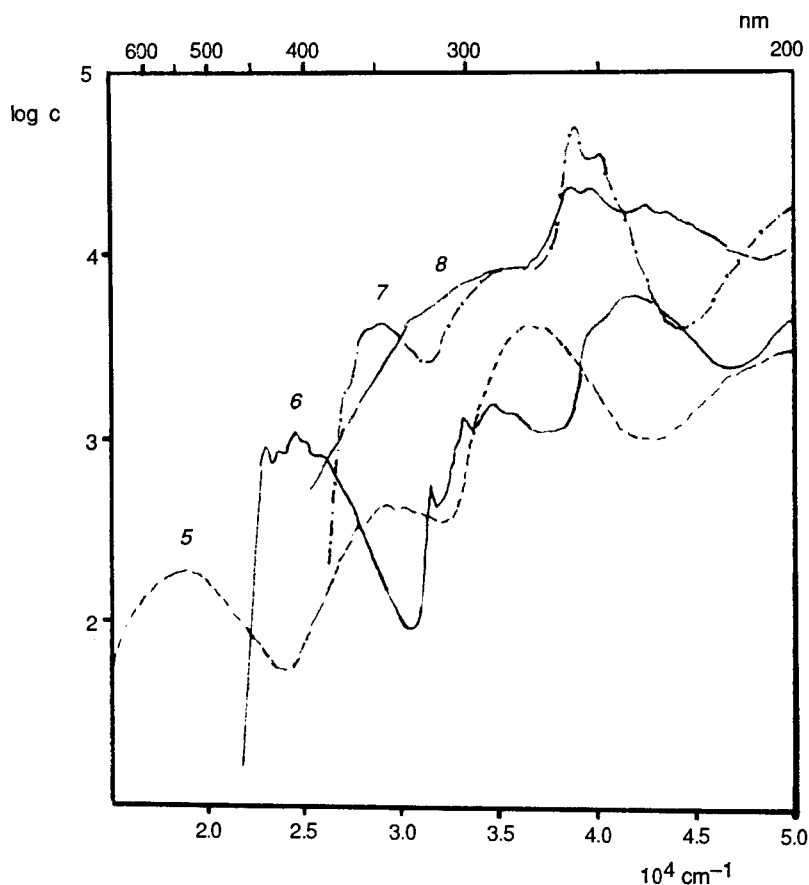


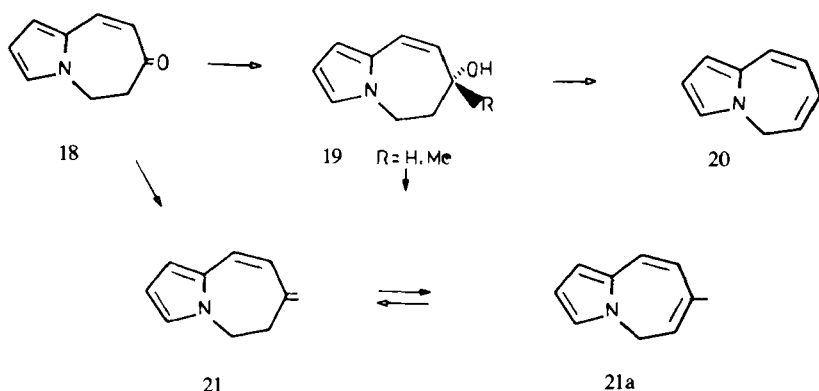
FIG. 2. Ultraviolet spectra of 4-azaazulenones (5–8).

Ultraviolet spectra of 4-azaazulenones 5–8 (shown in Fig. 2), have been compared with Pariser–Parr–Pople (PPP) calculations (85MI2, 85UP1). The special role of 4-azaazulen-3-one (5) deduced from the $^1\text{H-NMR}$ spectrum is reflected here in a long-wave maximum at 540 nm (see Table I for Hückel HOMO–LUMO gaps and REPE values).

III. Reactions

A. TAUTOMERISM

Four tautomeric benzo-4-azaazulenes (17a–d) are conceivable. Thermolysis of *o*-benzylphenyl azide gave 17b ($R = \text{H}$) and not, as had been previously thought (68JOC4286), isomer 17a ($R = \text{H}$) (70JCS(C)1490). Compound 17d



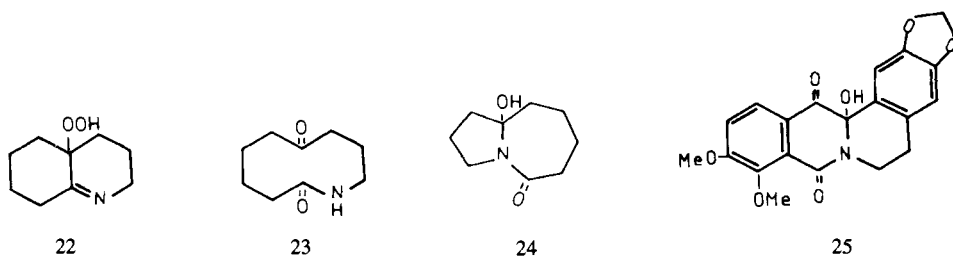
SCHEME 2

(R = H) was obtained from **17b** (R = H) by flash vacuum pyrolysis at 500°C (83CC1277).

o-(Trimethylbenzyl)phenyl azide decomposed at 190°C to give the three isomers **17b–d** (R = CH₃) in substantial amounts. A strong peri interaction in the 5-*H*-isomer (**17d**) (R = CH₃) was deduced from a comparison of the ¹H-NMR spectra of isomers forcing the 5-methyl group into a quasiaxial position (71JCS(C)3418).

The carbinol **19** (R = H) was obtained from a reduction of ketone **18** with borohydride (Scheme 2). Compound **19** was then dehydrated with *p*-toluenesulfonic acid to give the 5*H*-azaazulenone **20**, whose structure was proved by NMR spectroscopy. A mixture of approximately equal amounts of **21** and **21a** was formed by acid-catalyzed dehydration of **19** (R = CH₃). Wittig olefination of **18** gave the exomethylene derivative **21**, which on isomerization with potassium *t*-butoxide in dimethyl sulfoxide (DMSO) gave a mixture of 60% **21** and 40% **21a**. Surprisingly, no isomers of type **17b/c** were observed (82JCS(P1)1123).

Rearrangement of the hydroperoxide of Δ¹⁽⁹⁾-octahydroquinoline (**22**) was shown to proceed via the keto amide **23**, which in a transannular reaction gave the 4-azaazulenone **24** (55JA6595). Ring-chain isomerizations have

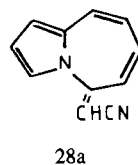
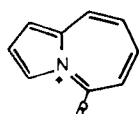
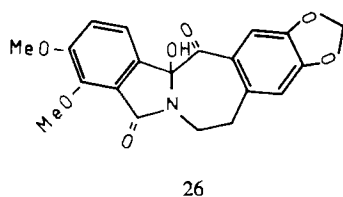


proved useful in the berberine field. Compound **25** gave **26** on treatment with ammonia in chloroform (79JOC4343). Compound **26** has been found in *Berberis empetrifolia* (82TL39).

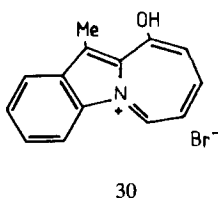
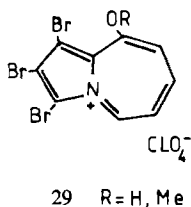
Isomerizations such as that of **23** into **24** and **25** into **26** need catalysis, since tautomeric forms of this type are stable and do not equilibrate in solution. The transformation of **25** to **26** reflects a general rule stating that five-membered hydroxylactams are more stable than six-membered isomers (85MI1).

B. PROTONATION YIELDING 4-AZAAZULENIUM SALTS

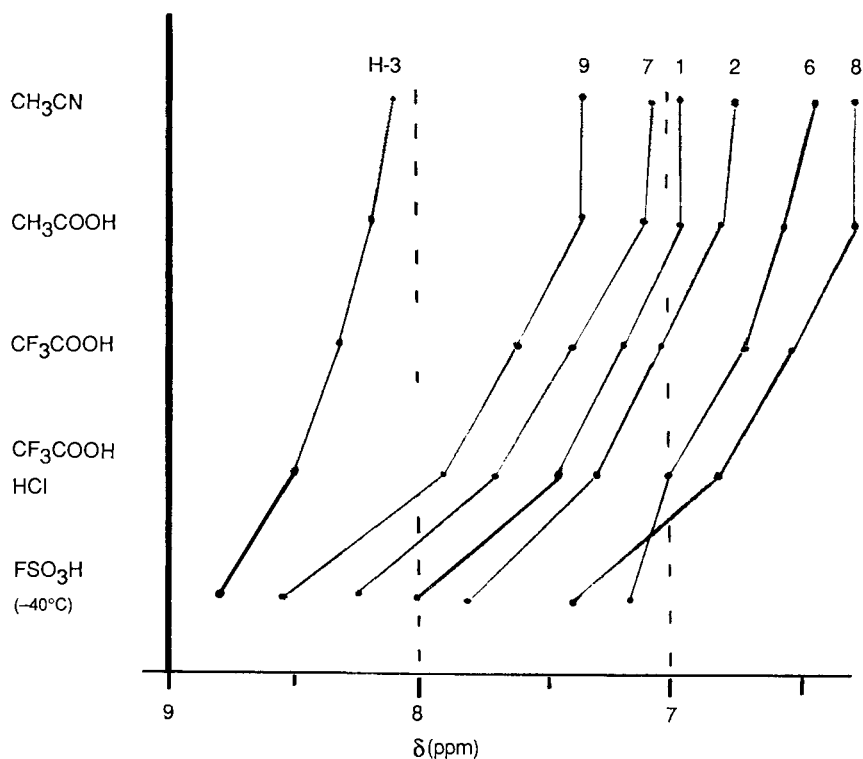
The 4-azaazulenium cation **27a** should be stable and aromatic. In spite of many attempts, it has not yet been obtained. 5-Cyanomethyl-4-azaazulenium perchlorate (**27b**), resulting from protonation of the conjugate base **28** (73CB1993), was shown by $^1\text{H-NMR}$ spectroscopy to be completely delocalized (78CB2407).



Substantial perturbations of the azaazulenium π -system are to be expected from hydroxy groups in protonated 4-azaazulenones. Salts **29** ($\text{R} = \text{H}$ and Me) were obtained from **11** by protonation and reaction with Meerwein's salts, respectively (69JCS(C)1028). The benzo derivative (**15**) gave salt **30** upon protonation with dry HBr (68TL1935).



In solvents of increasing acidity, $^1\text{H-NMR}$ spectra of 4-azaazulenones **5** (86MI1), **6** (78CB2407), **7** (82JCS(P1)1123; 86MI1), and **8** (78CB2407) reveal increasing high-field shifts of ring protons together with a diminution of differences of vicinal coupling constants in the seven-membered ring. A typical example given in Fig. 3 shows that complete protonation occurs in fluorosul-

FIG. 3. Protonation of 4-azaazulen-5-one (6); ^1H -NMR spectra.

fonic acid, the anisotropy of the carbonyl group being abolished as reflected in the chemical shift of proton H-6 (78CB2407).

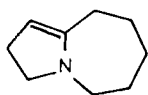
Information on differences in basicity of 4-azaazulenones was obtained from NMR spectra in CDCl_3 and trifluoroacetic acid (TFA). An alteration of the average shift of ring protons on going to the acetic solvent (see Table III) was thought to reflect differences in basicity. Thus, the order $5 > 7 \gg 8 > 6$ has been established (86M11).

TABLE III
AVERAGE CHEMICAL SHIFTS (δ) AND THEIR DIFFERENCE
($\Delta\delta$) OF A RING PROTONS IN 4-AZAAZULENONES (5-8)^a

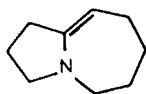
Solvent	5	6	7	8
CDCl_3	6.01	6.95	6.74	6.79
$\text{CF}_3 \cdot \text{CO}_2\text{D}$	7.45	7.24	7.69	7.41
$\Delta\delta$	1.43	0.25	0.95	0.62

^a (86M11).

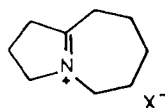
C. OXIDATION



31a



31b



32

Treatment of perhydro-4-azaazulene (**3**) with mercuric acetate produces a mixture of dehydro derivatives **31a** and **31b**, which, with acids, yields homogeneous salts of structure **32** (56JOC344). The enamine **34**, which was obtained by the same route from **33**, served as a model compound in a study of the synthesis of cephalotaxine (72JOC3691). A reaction with ethyl γ -bromoacetoacetate surprisingly yielded the quinolizidine **36**, which was formed by rearrangement of the intermediate annellation product **35** (Scheme 3). Phthalimides **38** were obtained from a Baeyer–Villiger oxidation of 4-azaazulen-3-ones **37** (77JOC1093).

Ozonolysis of the $\Delta 8$ -double bond in **39** gave the diacetal **40**, which was transformed into the parent antitumor antibiotic **41** by conventional routes (85H1603). Attempts to obtain **41** by rearrangements of derivatives of the keto amide **42** (e.g., the oxime), failed.

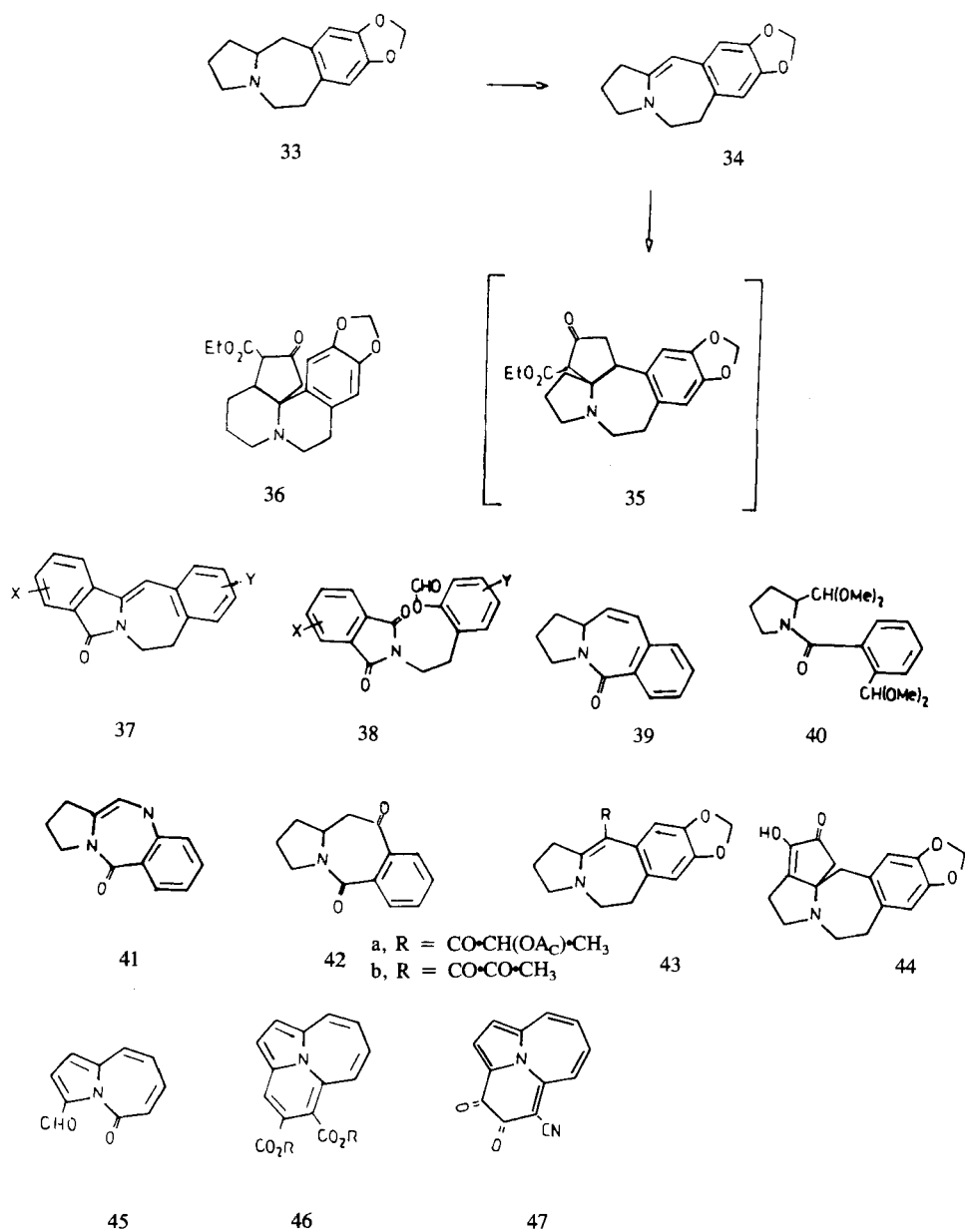
D. REACTIONS WITH ELECTROPHILES AND NUCLEOPHILES

Treatment of enamine **34** with 2-acetoxypropionyl chloride in the presence of suspended sodium bicarbonate gave 75% of the vinylogous enamide **43a**, which upon hydrolysis and oxidation with lead tetraacetate was converted into the α -dicarbonyl compound **43b**. Compound **43b** with magnesium methoxide in methanol gave desmethylcephalotaxinone **44** (72JA7172), thus avoiding the rearrangement shown in Scheme 3 (72JOC3691).

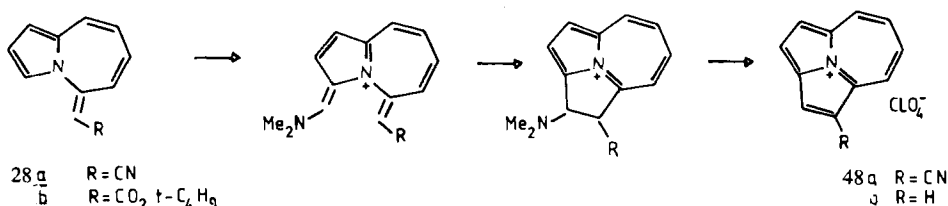
The aldehyde **45** has been obtained from a Vilsmeier reaction of 4-azaazulen-5-one (**6**). Compound **45** was subsequently transformed to the [2.3.4]cyclazine **46**. A twofold acylation of the azaazulene **28** with oxalyl chloride led to the [2.3.4]cyclazinequinone **47** (75CB2969; 79CB3577). [2.2.4]Cyclazinium salts **48** were obtained under Vilsmeier conditions from 5-methylene-4-azaazulenes **28** on a route shown in Scheme 4 (83CB1174).

A nucleophilic attack of hydrazine occurs at the 5-position of the azaazulenone **15**, followed by ring opening and formation of Δ^2 -pyrazoline **49** (70JCS(C)1490) (Scheme 5).

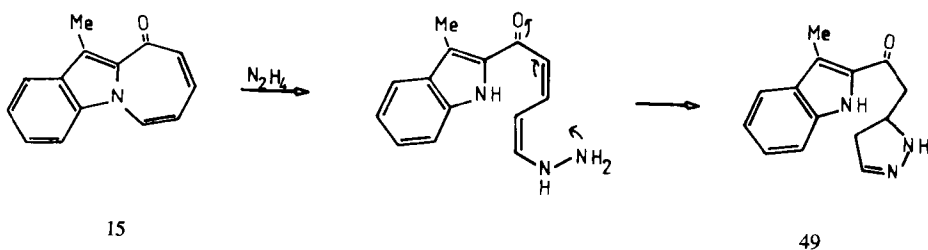
The reaction of **15** with hydrazine indicates two possibilities for nucleophilic attack at 4-azaazulenones **4–8**: (1) reaction at the carbonyl group and



SCHEME 3



SCHEME 4



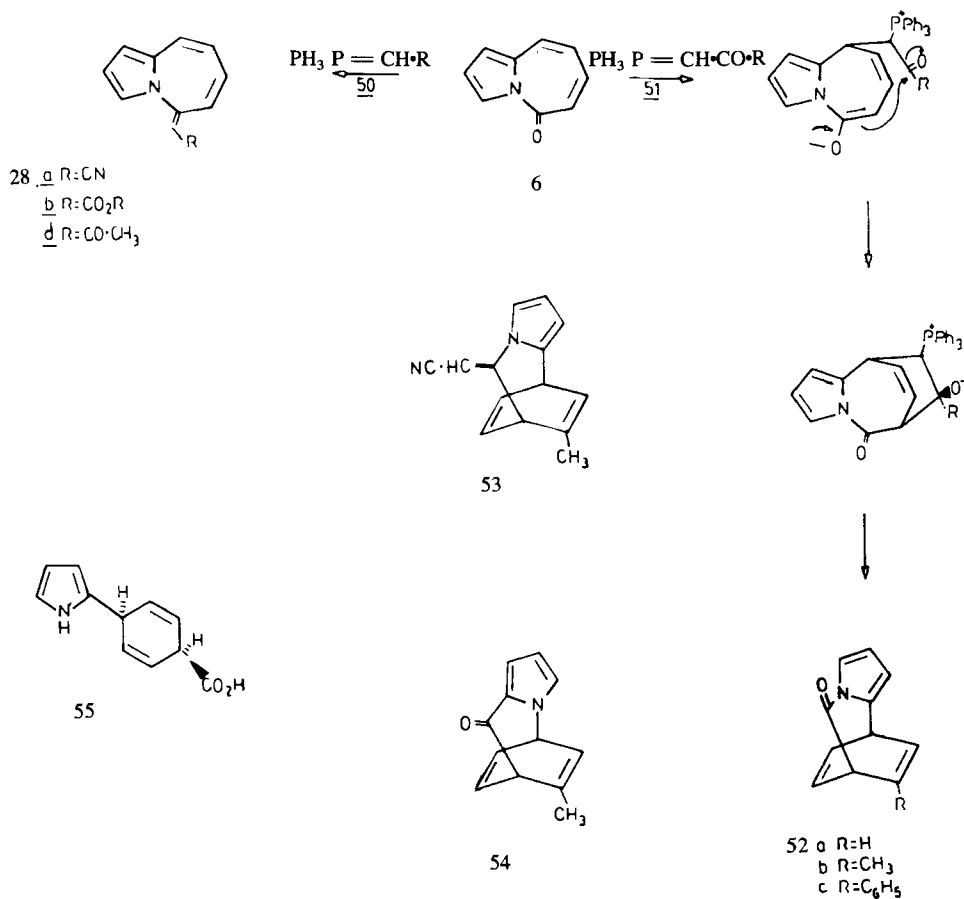
SCHEME 5

(2) a Michael addition at activated olefinic positions. Wittig reactions of 4-azaazulen-5-one (**6**) may serve to illustrate this (Scheme 6). Olefins **28** resulting from attack at the carbonyl group of **6** are obtained from reactions with alkoxycarbonylmethylenephosphoranes and cyanomethylenephosphoranes (**50**, R = CO₂R, CN). Turning to acylmethylenephosphoranes (**51**, R = H, CH₃, C₆H₅), however, one observes nucleophilic attack at the 9-position of **6**, yielding 20–50% of tricyclic compounds **52**; 38% of **52b** was obtained together with 1% of the olefine **28d**. The reaction, which is formally a Diels–Alder addition of a simple acetylene to a diene, was achieved also with **28a** (to give **53**) and azulenone **8** (yielding 53% of **54**). Hydrolysis of **52b** gave the interesting cyclohexadiene **55** (79TL4529; 81CB3146).

E. CYCLOADDITION REACTIONS

Steric control of the Diels–Alder reaction of the enone **56** has been reported (82H2053). The ene adduct **57** (4.5%) was obtained in a reaction with 1,3-bis(trimethylsilyloxy)butadiene at 180°C, together with the main product **58** (39.5%) resulting from an ene addition. Under the same conditions, the analogous indolizidine derivative **59** gave only ene adducts.

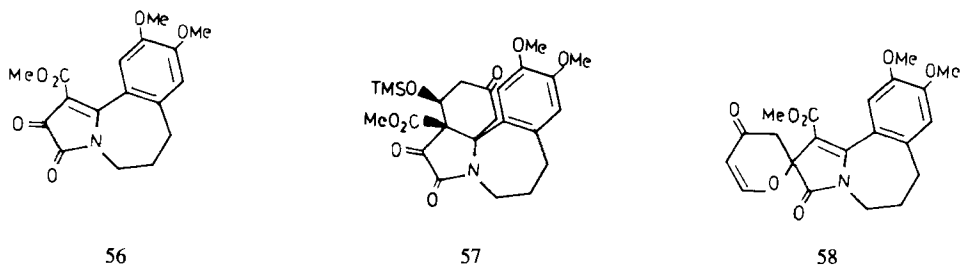
The unusual Diels–Alder reaction is obviously due to a nonplanarity of the aromatic and dioxopyrroline rings in **56**, thus causing steric hindrance to the

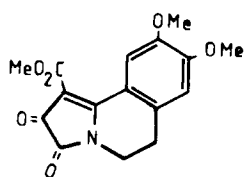


SCHEME 6

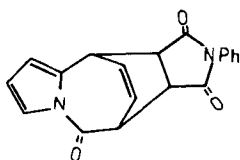
ene addition. In the six-membered congener **59**, however, the aromatic and dioxypyrroline rings are almost coplanar.

A (4 + 2)-adduct (**60**) was obtained in good yields from **6** and *N*-phenylmaleimide. A similar reaction of **28**, however, failed. Cycloadditions at the

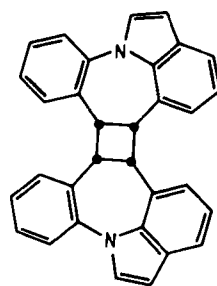




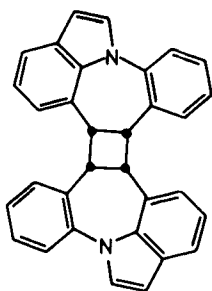
59



60



61



62

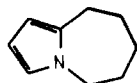
seven-membered ring of [2.3.4]cyclazines **46** as well as a dimerization have been observed (75CB2969).

Photodimerization of dibenzoazaazulene **10** gave only syn dimers **61** and **62**, with **61** favored in solid-phase dimerization and **62** predominating in solution. Eximers have been proposed to be responsible for the formation of syn isomers (84JOC2978).

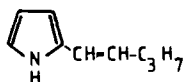
F. MISCELLANEOUS REACTIONS

Thermolysis of the partially hydrogenated 4-azaazulene **63** at 600°C gave two products; structures **64** and **65** have been proposed (62JOC1652).

Hofmann degradation of the quaternary base of the methylammonium salt of Schöpf's base IV (**66**) has been shown to lead to the olefin **67** and the macrocyclic amine **68** (73HCA553).



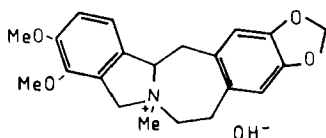
63



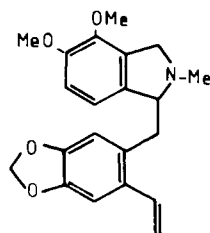
64



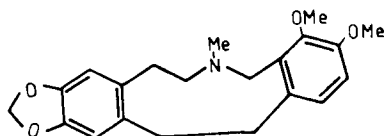
65



66



67

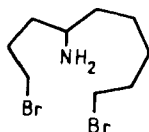


68

IV. Synthesis

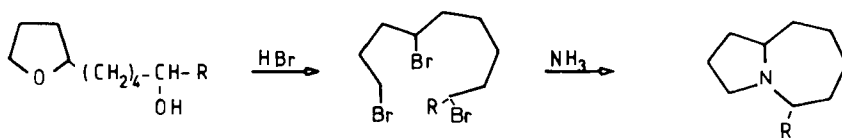
A. CYCLIZATION

1. Alkylation and Acylation at Nitrogen Atoms

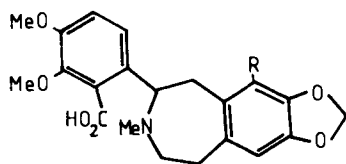


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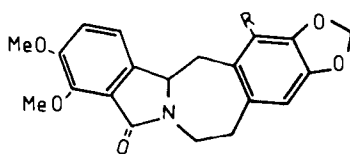
Perhydro-4-azaazulene (**3**) was obtained from an intramolecular alkylation of the primary amino group of **69** (39CB1638). A closely related route has been used to synthesize 5-substituted derivatives of **3**, as shown in Scheme 7 (53M777).



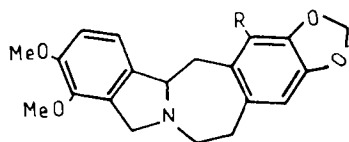
SCHEME 7



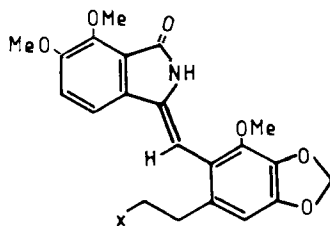
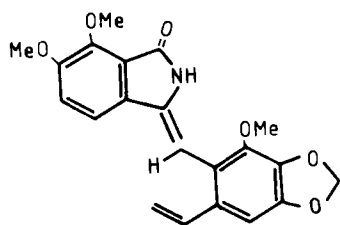
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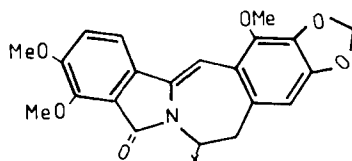
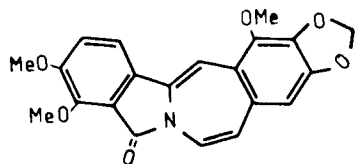
71 R = H, OMe



72 R = H, OMe

73 a x = N⁺Me₃ J⁻b x = NMe₂ → O

74

75 x = OH, OAc, NMe₂, OEt

76

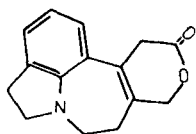
N-Demethylation and acylation of the azepines **70** with acetic anhydride gave γ -lactames **71** in high yield; they were transformed into Schopf's bases IV (**72**) by treatment with B_2H_6 (72CJC2022).

Thermal decomposition of narceine imide methiodide **73a** in the presence of 30% aqueous potassium hydroxide afforded 91.4% of a mixture of *Z/E*-narceone imides **74**, along with the azaazulenone **75** ($R = OMe$) (1.5%), which was also formed (8%) from **74** under the same conditions (75CCC681).

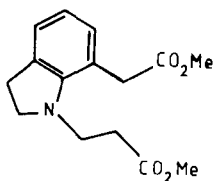
From a Polonowski reaction of narceine imide *N*-oxide **73b** *N*-bridgehead bicycles **75** were obtained containing functional groups in the 5-position. Reaction of **75** ($R = OAc$) with ethanolic sulfonic acid gave **75** ($R = OC_2H_5$), together with the azaazulen-3-one derivative **76** (82MI1).

2. Condensation and C-Alkylation

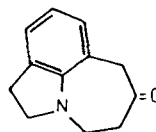
In the course of a synthesis of apo- β -erythroidine **77**, the tricycle **79** was prepared by ester condensation of **78**, followed by removal of the ester group (66JA4061).



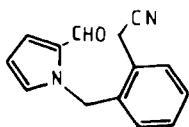
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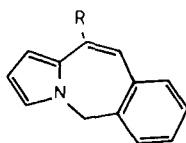
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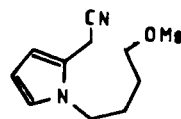
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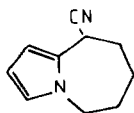
80



81a $R = CN$
81b $R = H$



82



83

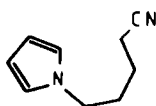
Good yields of the 5*H*-4-azaazulene **81a** were obtained from **80** by intramolecular condensation. The functional group was removed by hydrolysis and thermal decarboxylation to give the parent compound **81b** (79JHC1443). In a closely related alkylation reaction, tosylate **82** was transformed into nitrile **83** (82CJC2295).

3. Friedel–Crafts Type Reactions

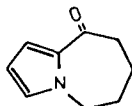
Nearly all of the cyclization reactions covered in this section aim at formation of the seven-membered ring. A distinction can be made between acylations at pyrrole rings and Friedel–Crafts type cyclizations at benzene rings.

A modified Houben–Hoesch reaction of the nitrile **84** gave 31% of the azaazulenone **85**, which was transformed to **63** by Wolff–Kishner reduction (62JOC1652). Similarly, **86** has been converted into **87** (78CB2407). Acid **88** gave ketone **89** with polyphosphoric acid (69JCS(C)1028); as was **91** formed from **90** (79JHC1443).

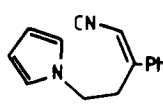
A five-membered ring is formed in a Friedel–Crafts cyclization of **92** to give **93** (68T2645). The acid **94** gave ketone **95** on treatment with polyphosphoric



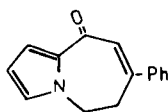
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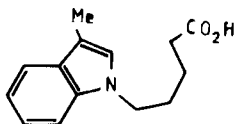
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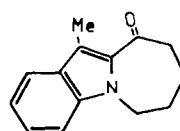
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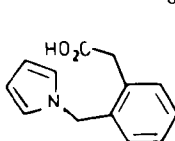
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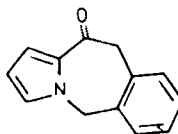
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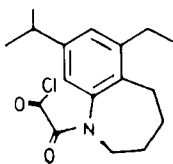
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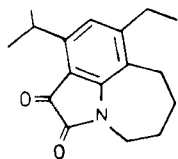
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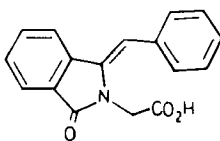
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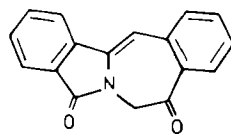
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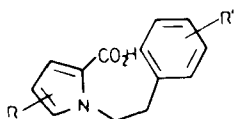
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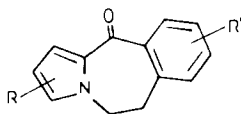
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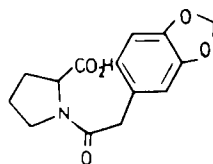
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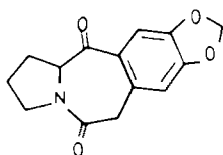
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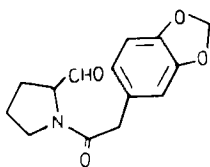
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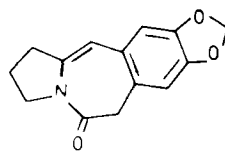
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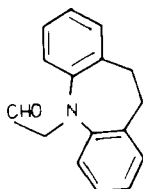
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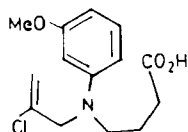
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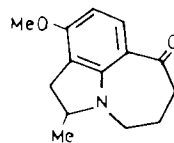
101



102



103



104

acid (79JCS(P1)1547), and the cyclization of pyrrolecarboxylic acids **96** to 4-azaazulenone derivatives **97** was achieved with trifluoroacetic anhydride and tin tetrachloride (76JOC875) or aluminum chloride (83JOC3220, 83JOC3234).

Cyclization with polyphosphoric acid of **98**, obtained from proline, to give the dioxo derivative **99** is part of a stereoselective synthesis of (\pm)-cephalotaxine and its analogue (86TL2023).

Aldehyde **100** was cyclized to the tetracyclic enamide **101** in chloroform containing boron trifluoride at room temperature in 87% yield (75JA2503). A similar cyclization of aldehyde **102** was brought about with molecular sieves at room temperature to give 69% of the dibenzo-4-azaazulene **10** containing a fully conjugated π -system (82H75).

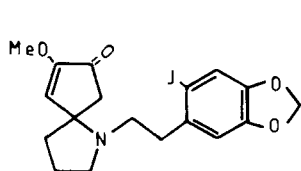
Heating of **103** to 110°C gave the azaazulene **104** in a twofold cyclization, albeit in low yield (75JCS(P1)1446).

4. Cyclization via Reactive Intermediates

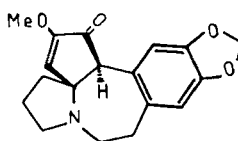
The crucial step in a synthesis of *Cephalotaxus* alkaloids developed by Semmelhack is a ring closure of spirocyclic compound **105**, leading to cephalotaxinone **106**. Several methods have been applied successfully, including nucleophilic addition to a transient aryne (15%), coupling via a σ -arylnickel complex (30%), and addition to a transient aryl radical generated from alkali metal reduction (45%) or by irradiation (94%) (75JA2507). Stereoselective formation of the epimer **106** has been discussed (72JA8629).

Cyclization reactions of α -acyliminium ions with allyl- and propargylsilanes constitute a useful method for the preparation of various N-bridgehead bicyclic systems. Thus, from a reaction of hydroxylactams **107** and **108**, the azaazulenes **109** and **110** were obtained in excellent yields (83TL1407). Similarly, the keto amide **112** was obtained from the imide **111** by reduction to the corresponding hydroxylactam and acid-catalyzed cyclization (84JCS(P1)2477).

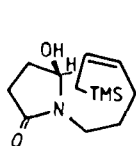
Thermal decomposition of phenyl azides generally leads to five-membered ring structures. In cases where cyclization is not possible, ring enlargement of a phenyl to form azepines has been reported (59CB2961). Thermolysis of *o*-azidodiphenylmethane in 1,2,4-trichlorobenzene at 160°C gave 66% of a benzoazaazulene initially thought to be **17a** ($R = H$) (68JOC4286) but later shown to have structure **17b** ($R = H$) (70JCS(C)1490). Thermolysis of a number of *o*-benzylphenyl azides substituted in the benzyl group has been shown to result in formation of substituted azaazulenes **113**. When an *o*-methoxy group was present on the benzyl ring, major products were acridines and acridanes. The nitrene route was successfully applied in other cases (74JCS(P1)2066) (78JCS(P1)1211). 1-(*o*-Azidophenyl)-1-phenylethanol (**114**)



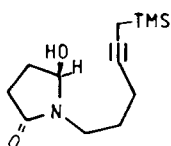
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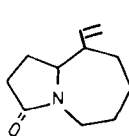
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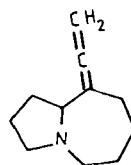
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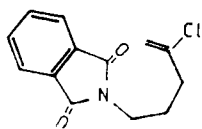
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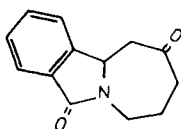
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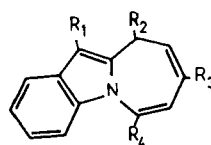
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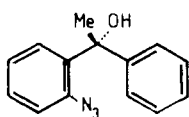
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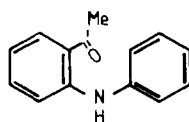
112



113 $R_1 - R_4 = H$; $R_1 = Me$, $R_2 - R_4 = H$;
 $R_3 = Me$; $R_1, R_2, R_4 = H$;
 $R_4 = Me$; $R_1 - R_3 = H$, $R_2 - R_4 = Me$;
 $R_1 = H$; $R_4 = OMe$; $R_1 - R_3 = H$;
 $R_2 = OMe$, $R_1, R_3, R_4 = H$.



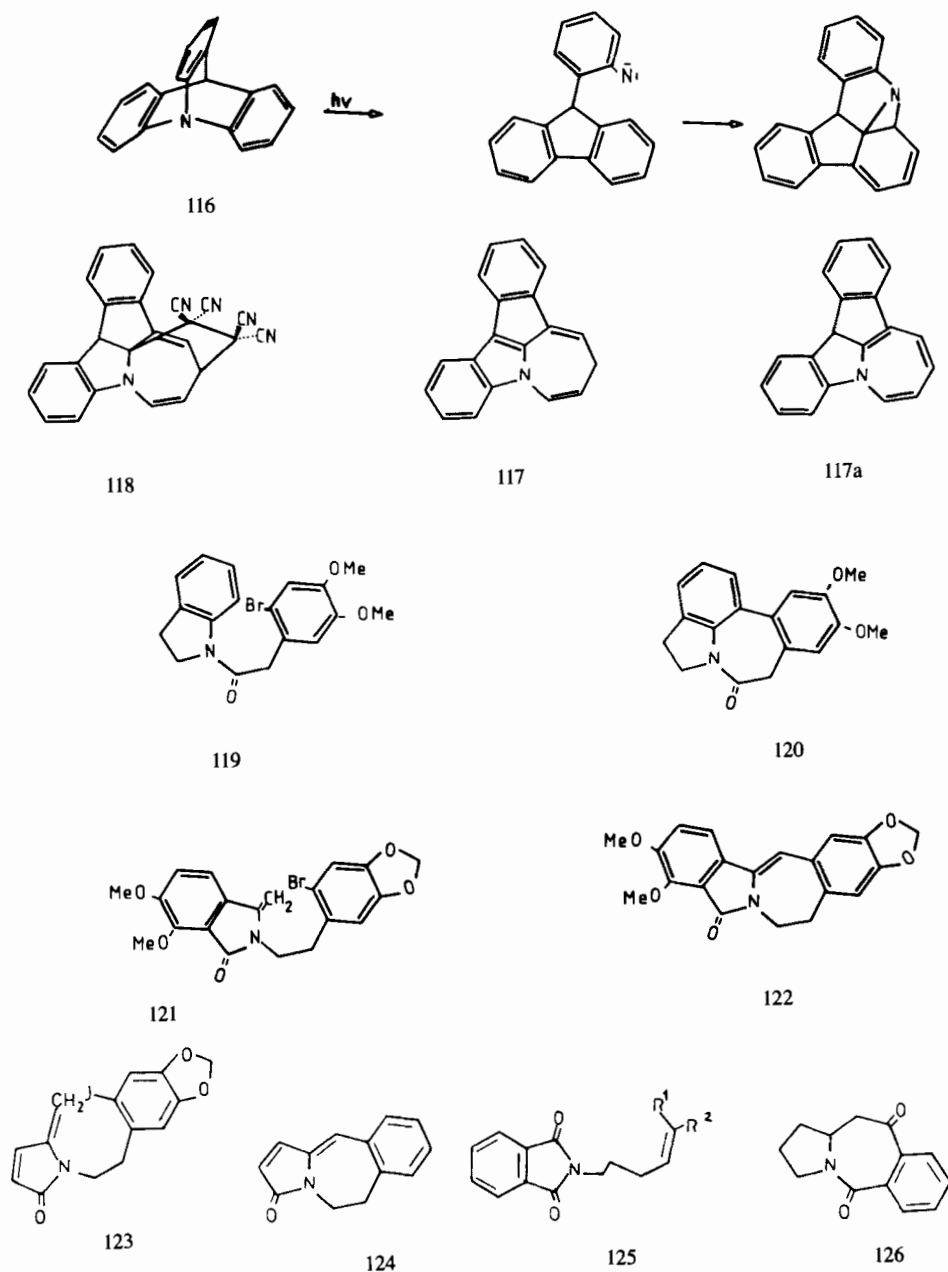
114



115

decomposed to give *o*-anilinoacetophenone (**115**); the reaction has been explained mechanistically (71JCS(C)3418). Flash vacuum pyrolysis of *o*-azidodiphenylmethanes gave acridanes and acridines, in contrast with the formation of azaazulenes **113** at lower temperature in solution (83CC1277).

A nitrene has been generated by photolysis of 1-azatriphitycene (**116**), which gave the tetracycle **117** by a route shown in Scheme 8. The intermediate **117a** was intercepted with tetracyanoethylene (TCNE) to give **118** (85JA1329).



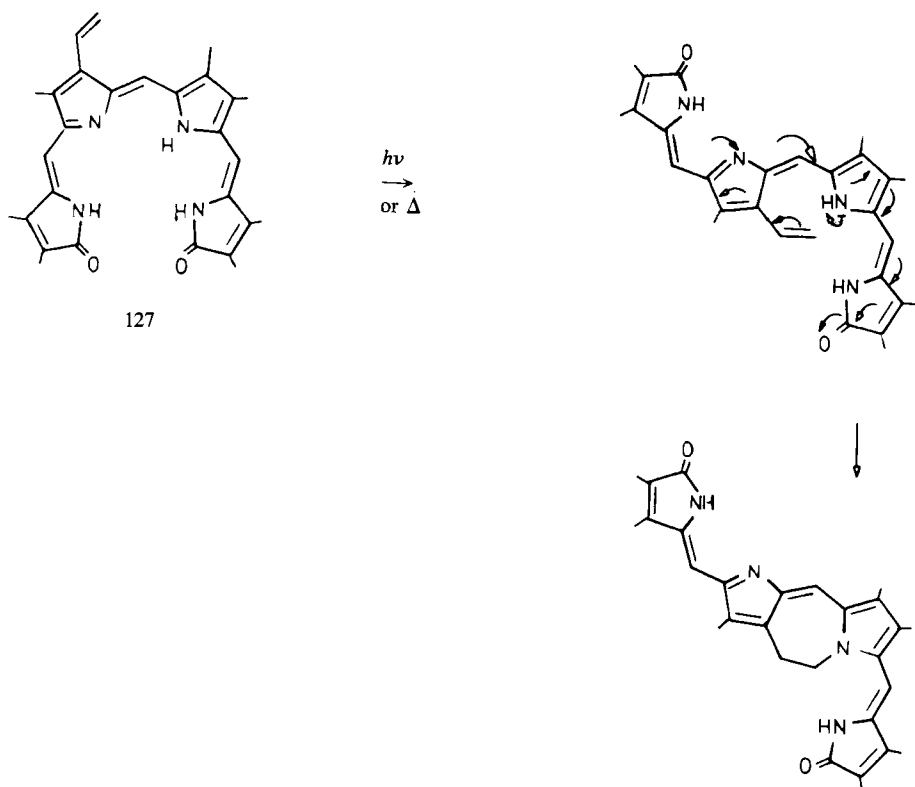
SCHEME 8

5. Photocyclization

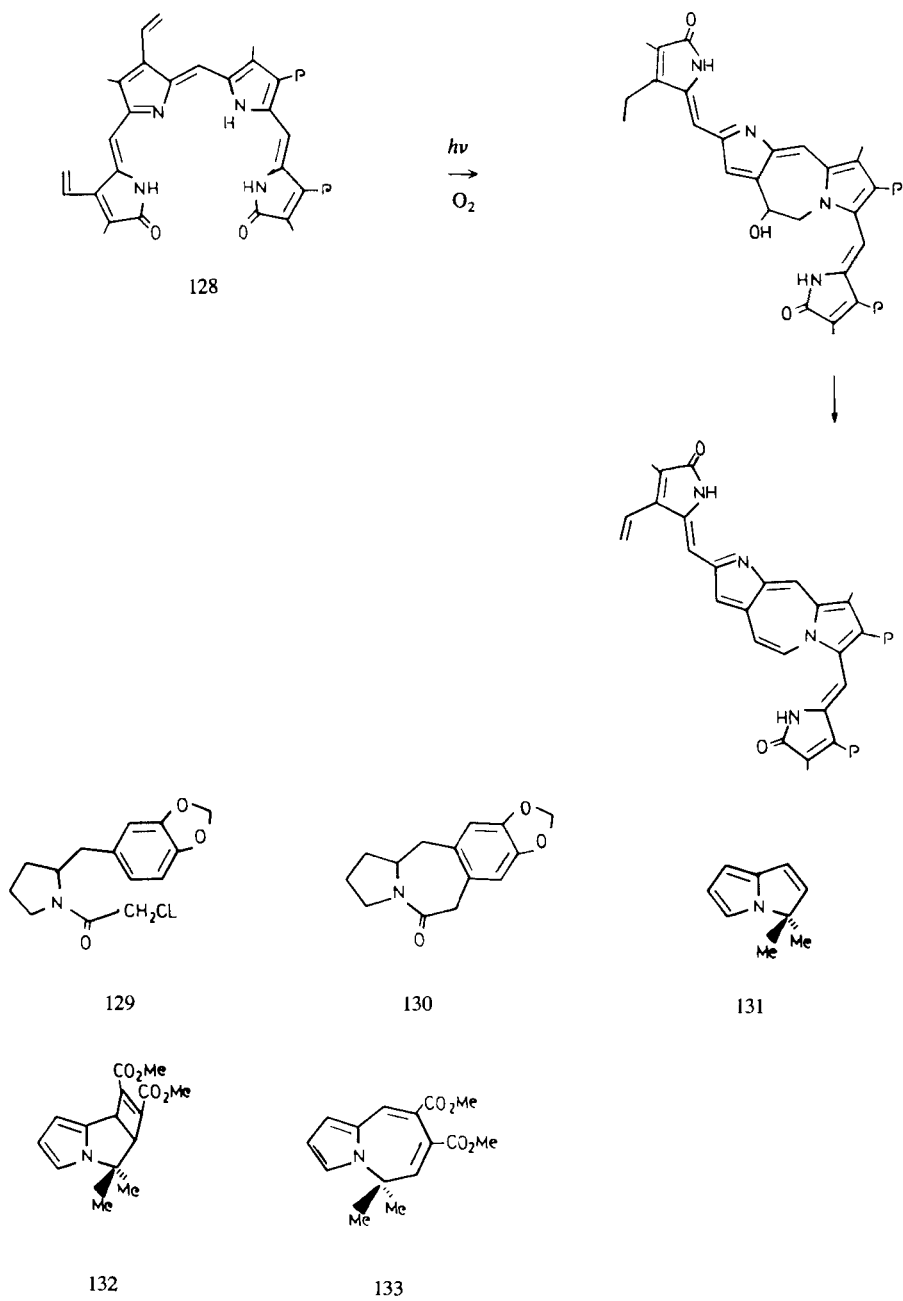
Photochemical formation of a biphenyl linkage in **119** to give the tetracyclic compound **120** could be achieved in 4.4% yield (72TL5031). A photocyclization of the phthalimidine **121** to **122**, which subsequently transformed into Schopf's base IV (**71**) ($R = H$), proceeded in 21.5% yield (71TL4867). Similarly, **123** reacted to give the *Cephalotaxus* alkaloid synthon (**124**) (76CC505).

A photochemical reaction of *N*-alkenylphthalimide **125** ($R_1 = R_2 = H$) in acetonitrile gave **126**, resulting from intramolecular skeletal reorganization via N—C bond scission and cyclization (78CL769). Stereochemistry of the transformations of **125** ($R_1, R_2 = H, Me$) has been studied (85JCS(P1)2025) and mechanistic investigations have been reported (83JOC2981).

Photochemical and thermal isomerization and cyclization in bile pigments lead to 4-azaazulene derivatives. In Scheme 9, a proposed mechanism for the



SCHEME 9



SCHEME 10

cyclization of biliverdine IX γ or IX δ (**127**) is given (78H677). In the presence of oxygen, fully conjugated chromophores are formed. This is shown in Scheme 10 using irradiation of biliverdine XI δ dimethyl ester (**128**) (500–700 nm, DMSO) as an example (80HCA1098).

Photolytic cyclization of the chloroacetamide **129** afforded the azaazulenone **130** in 25% yield (72JOC3691). Irradiation of a benzene solution of the pyrrolizine **131** and dimethyl acetylenedicarboxylate (DMAD) gave a 26% yield of the 1:1 photoadduct **132**, which on heating at 180–200°C gave 61% of the azaazulene **133** (72JCS(P1)2517).

6. Cycloadditions

3*H*-Pyrrolizines **134** have been transformed into bismethylenepyrrolizinium salts **135**, which show a propensity to cycloaddition reactions (Scheme 11). Thus, from a reaction with sodium cyclopentadiamide, tetracyclic cyclazines **136** were obtained (70CC790; 83CB1174). [2.3.4]Cyclazinium salts **137a,b** resulted from a reaction of **135** with vinyl ethyl ether and morpholinocyclopentene, respectively (83CB1174).

Vilsmeier bases **138a** (74JHC811) and **138b** (76H957) gave 4-azaazulene derivatives **139** on reaction with dimethyl acetylenedicarboxylate (ACDE).

2-Alkoxy-3-azaazulenes **140** reacted with ACDE to give the annellated 4-azaazulene derivative **141** (81BJC1277).

7. Miscellaneous Cyclizations

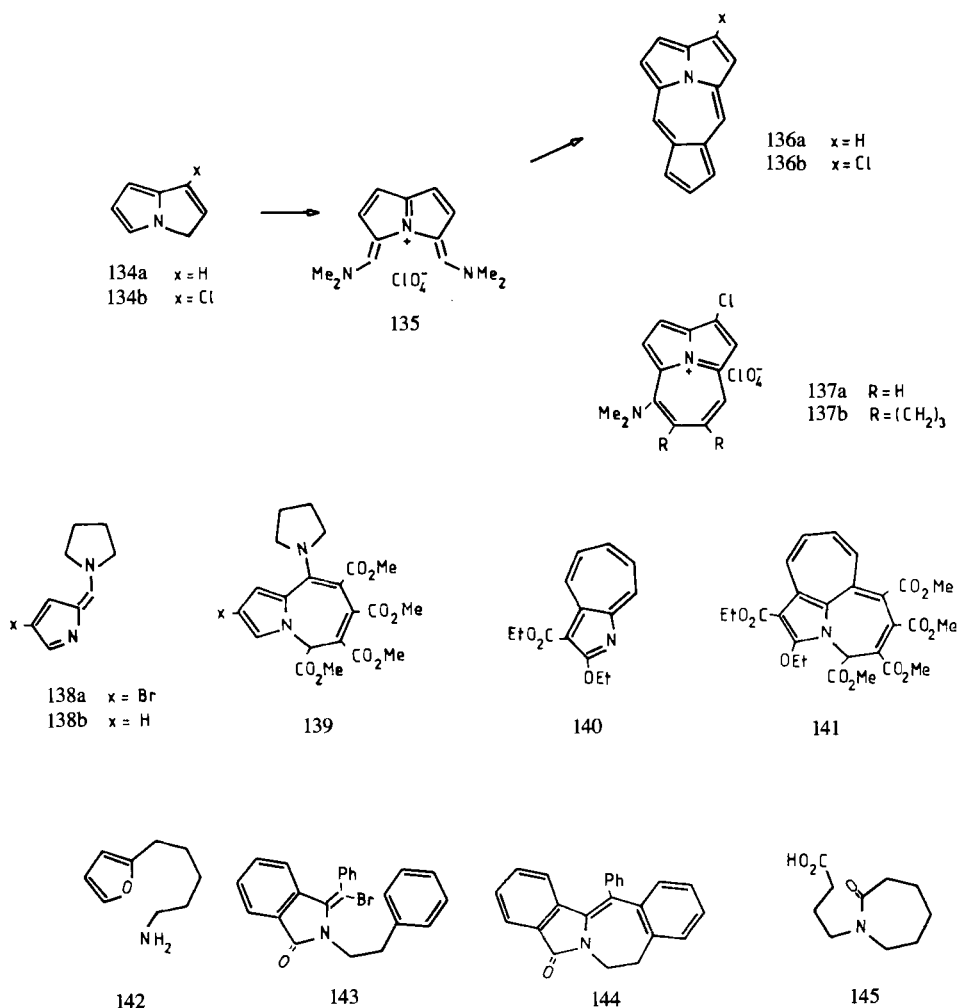
The 4-azaazulene derivative **63** has been synthesized in 14% yield by cyclo-dehydration of furylpentylamine (**142**) over alumina at 400°C (62JOC1652).

Treatment of the phthalimidine **143** with KOH in boiling ethylene glycol gave 10% of the dibenzoazaazulene **144** (69TL887).

A simple efficient synthesis of the bicyclic enamine **31** (95%) by distillation of the ω -carboxyalkyllactam **145** from soda lime seems to be a variant of the classical Ruzicka cyclization of dicarboxylic acids (83CJC2016).

B. REARRANGEMENTS

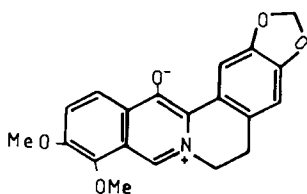
As shown in Section I, Clemmensen reduction of quinolizidin-1-one (**1**) gave perhydroazaazulene (**3**) instead of the expected quinolizidine (**2**). The mechanism of this rearrangement has been studied and the reaction has been used for a synthesis of azaazulene derivatives (61MI1).



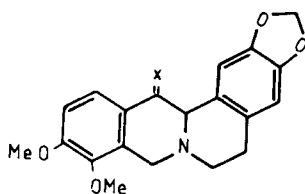
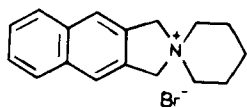
SCHEME 11

The tetracyclic base, obtained as a minor product by reduction of monooxyberberine **146** with zinc and acetic acid (63M11), was shown by Schöpf to be the isomer **72** ($R = H$) of the main product tetrahydroberberine **147a**. Commonly referred to as Schöpf's base IV, **72** ($R = H$) is of interest because of its relationship with papaverubine alkaloids (70M11).

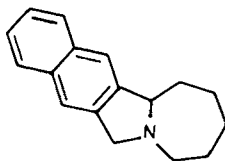
Schöpf proposed a ketone (**147b**) as an intermediate in the formation of **72** ($R = H$), which might similarly rearrange to the quinolizidinone (**1**) during Clemmensen reduction (65CB2566).



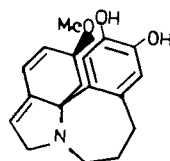
146

147a $x = H_2$ 147b $x = O$ 

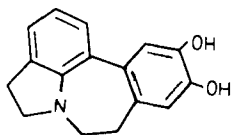
148



149



150

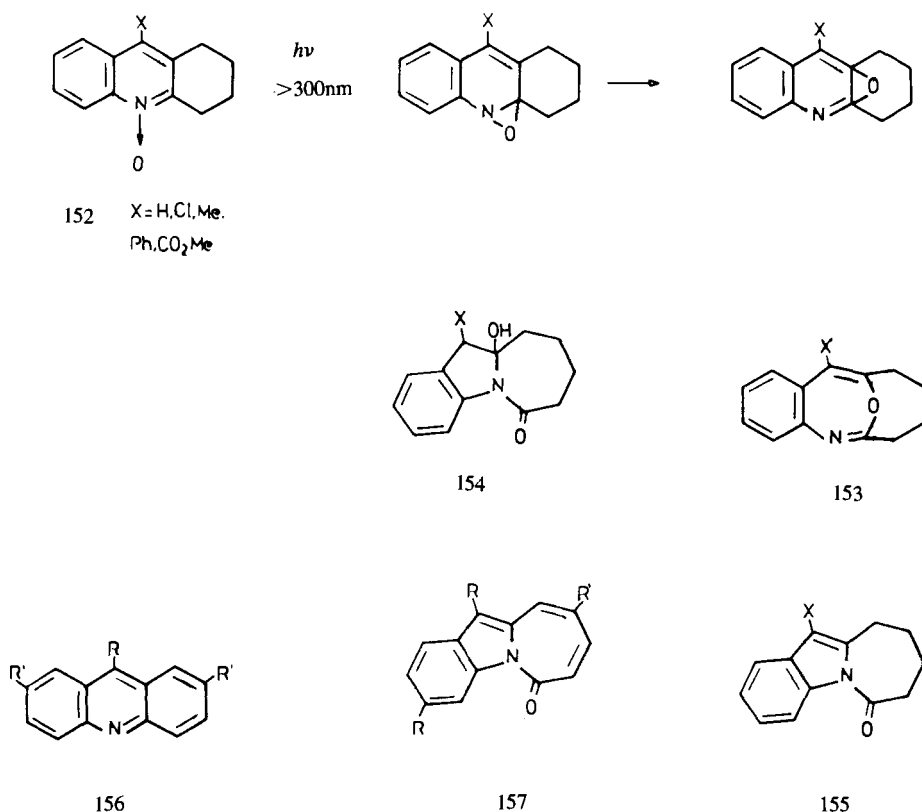


151

During an investigation of a Stevens rearrangement, a conversion of the spirocyclic ammonium salt **148** into the tetracyclic **149** was found to occur on treatment with phenyllithium (54LA(589)55).

Erysopine I (**150**) on heating in hydrobromic acid rearranges to apoerysopine **151** (51HCA1601, 51JA589), which was also synthesized by conventional routes (64TL1729). A similar rearrangement of erythroidine **186** is described in Section V.B.

Irradiation of *N*-oxides **152** yielded benz[*d*]-1,3-oxepines (**153**). Compounds **153** were unstable to moisture, hydrolyzing to **154** during chromatography (Scheme 12). Hydroxylactams **154**, formed in 45–70% yield, were transformed nearly quantitatively into **155** (69CPB1290). Attempts to obtain 4-azaazulenones **157** from acridine *N*-oxides **156** by this route have met with only limited success; the main products were dibenzooxaazepines (79TL1273).



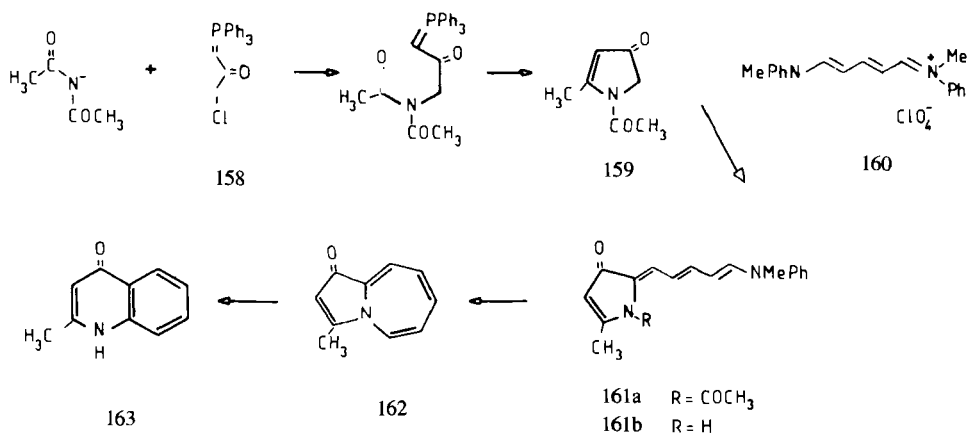
SCHEME 12

C. SYNTHESIS OF 4-AZAAZULENONES (4-8)

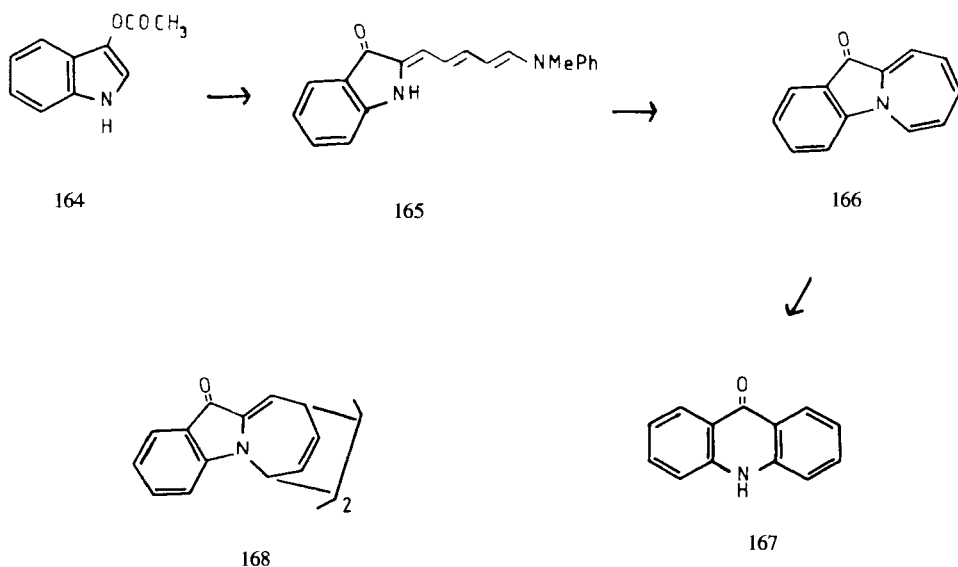
The synthesis of 4-azaazulenones is treated in a special section because of the similarities of the synthetic methods as well as the properties of the topologically correlated π -systems. Benzo derivatives with additional substituents that do not fit the relations were covered in preceding sections.

The starting compound for a preparation of the 4-azaazulen-1-one **162** was *N*-acetyl-3-oxo-5-methylpyrroline (**159**), which could be obtained from diacetylamine and the chlorophosphorane **158** in a two-step reaction. Condensation of **159** with Zincke's salt (**160**) gave **161a**, which after saponification to **161b** gave 3-methyl-4-azaazulen-1-one (**162**) upon heating. Compound **162** is highly colored and rearranges easily to give the quinolone **163** (Scheme 13).

Attempts to prepare the benzo derivative **166** by the same route (Scheme 14)



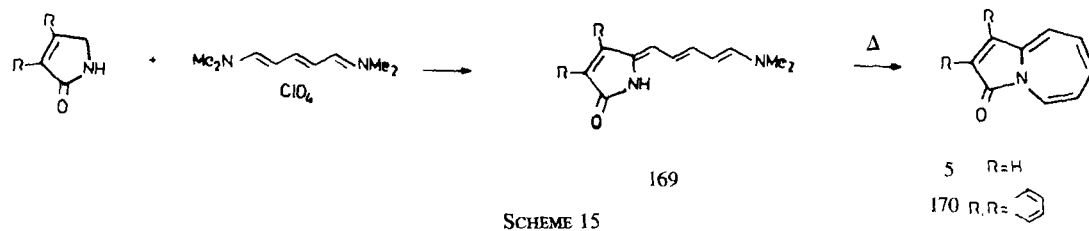
SCHEME 13



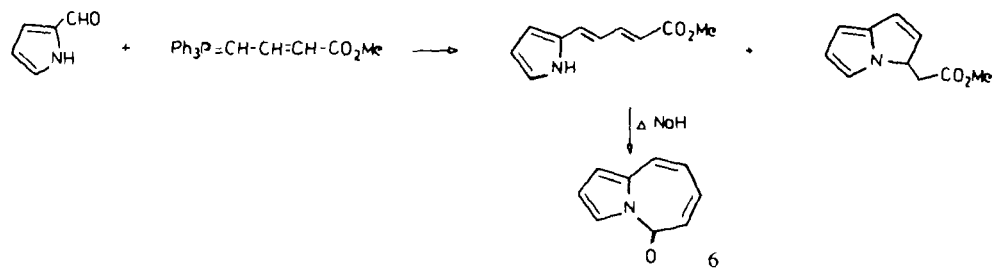
SCHEME 14

gave only the rearranged acridone **167**, together with a dimer (**168**) of the benzoazaazulene derivative (86MI1).

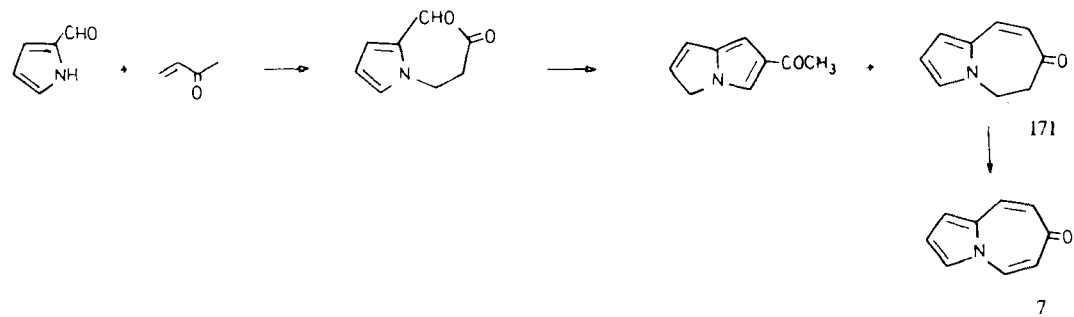
4-Azaazulen-3-one (**5**) and its benzo derivative (**170**) were obtained from Δ^3 -pyrroline-2-ones in a similar way (Scheme 15) (83MI1). Both of these 3-ones are highly colored and very unstable, in contrast to the isomeric 4-azaazulen-5-one (**6**), whose synthesis is shown in Scheme 16 (73CB1993).



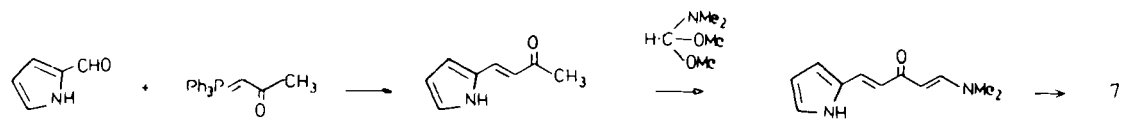
SCHEME 15



SCHEME 16

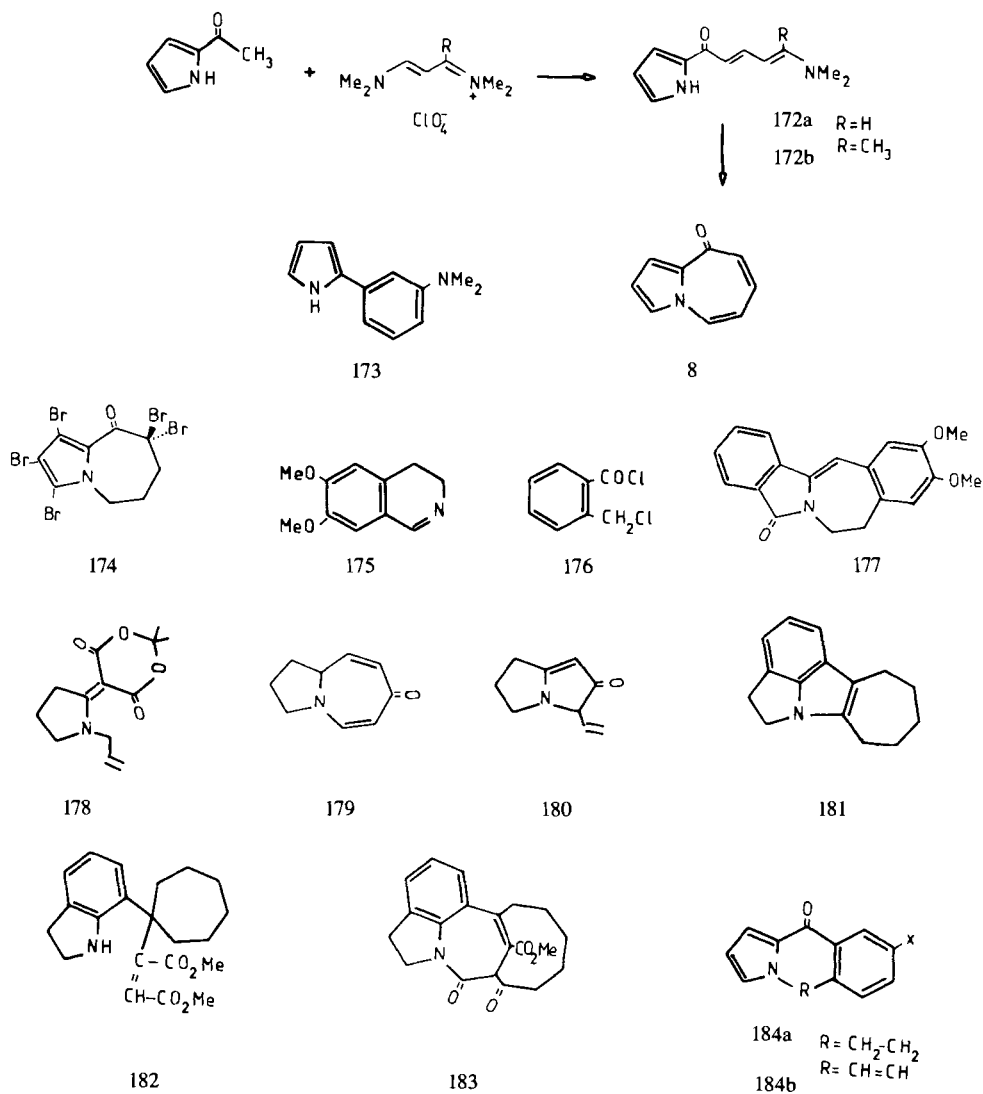


SCHEME 17



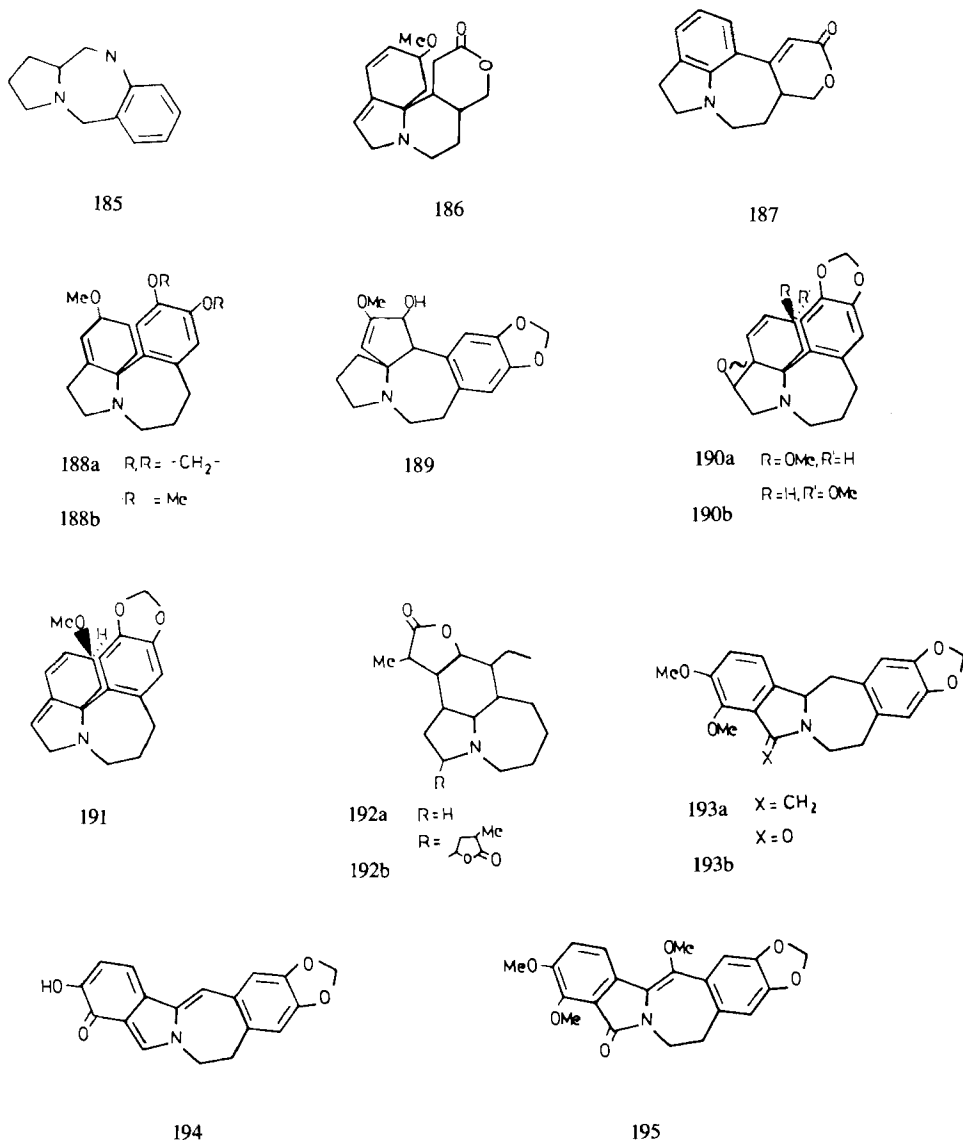
SCHEME 18

Two routes to 4-azaazulen-7-one (**7**) are known (Schemes 17 and 18). The crucial step of the first synthesis (Scheme 17) is the dehydrogenation of **171**, which is difficult to control (82JCS(P1)1123). Dehydrogenation is avoided in the second synthesis (Scheme 18), which allows an easy preparation of the azaazulenone **7** on a large scale (86MI1).



SCHEME 19

The synthesis of 4-azaazulen-9-one (**8**) is shown in Scheme 19. The final cyclization could be achieved in boiling quinoline as well as by flash vacuum pyrolysis. Interestingly, only the parent compound **8** was obtained. Attempts to synthesize a methyl derivative of **8** by thermolysis of **172b** led to the pyrrole **173** (78CB2407).



SCHEME 19 (continued)

D. MISCELLANEOUS METHODS

Dehydrobromination of **174** with lithium bromide in dimethylformamide gave the tribromo-4-azaazulenone **11** in good yield (69JCS(C)1028). In a one-pot synthesis, the lactam **177** was obtained from the dihydroisoquinoline **175** and the benzoyl chloride **176** (84TL3485).

A thermal fragmentation of the pyrrolidine **178** gave a mixture of a 4-azaazulenone (**179**) and a pyrrolizidinone (**180**) (84TL833).

The structure of adduct **183**, obtained from the substituted indole **181** and ACDE, has been determined by X-ray crystallography. Evidence has been given for its formation via an unusual 1,3-shift of an acyl group in **182** (85JCS(P1)1921).

V. Applications

A. PRODUCTS OF PHARMACEUTICAL INTEREST

Benzo-4-azaazulenones **184a** were prepared as intermediates for potential central nervous system drugs (83JOC3220). The dehydro derivatives **184b** show a diverse profile of pharmacological properties, including antihistaminic, antiserotonergic, antidopaminergic, and oxigenic activity. Synthetic and receptor-binding properties have been reported (83JMC974).

Many derivatives containing the benzo-4,8-diazaazulene skeleton **185** show pronounced antitumor activities. Synthetic work in this field has been reported (85H1603).

B. NATURAL PRODUCTS

Since the chemistry of alkaloids derived from 4-azaazulenes is reported regularly (86MI2), only selected aspects will be presented from the natural product field. Structurally complex alkaloids such as flexicorine and rauflexine from *Rauwolfia* species (82JOC1732) are not mentioned.

In the course of investigating *Erythrina* alkaloids, treatment of β -erythroidine (**186**) with phosphoric acid gave a rearranged demethoxy derivative, apo- β -erythroidine (**77**), which was isomerized on alumina to give isoapo- β -erythroidine (**187**) (50JA2062). Compound **77** is of interest because of its own physiological activity. A synthesis is described in Section IV,A,2.

Two alkaloids possessing the 4-azaazulene skeleton have been isolated from leaves of *Dysoxylum lenticellare* (Meliaceae), namely 3-*epi*-schelhamericine (**188a**) and dihydrohomoerysotrine (**188b**) (83MI2). For a report on *Erythrina* and related alkaloids, see (84MI1).

Cephalotaxine (**189**) is a representative *Cephalotaxus* alkaloid; several ester derivatives, both natural products and semisynthetic ones, were found to exhibit significant antitumor activity (85MI3). Syntheses of cephalotaxinones **44** (Section III,D) and **109** (Section IV,A,4) have been mentioned.

Wilsonine (**190a**), epiwilsonine (**190b**), and fourtneine (**191**) have been isolated from *Cephalotaxus fortunei*. The structure of **191** was evaluated by spectroscopic methods (83P251).

Major alkaloids of *Stemona fuberosa* (Stemonaceae) are stemine (**192a**) (67CPB768) and tuberostemonine (**192b**) (68T2631), whose absolute configurations have been determined using NMR spectroscopy and X-ray crystallography (67CC460). A synthesis of a precursor (**93**) of **192** is given in Section IV,A,3.

From Berberiaceae, the closely related alkaloids **193**, **194**, **195**, (84T3957), **193a** (74TL599), and chilene (**26**) (82TL39) have been isolated.

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Hydrogenated Porphyrin Derivatives: Hydroporphyrins

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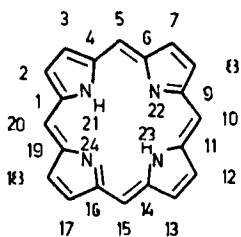
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I. Introduction

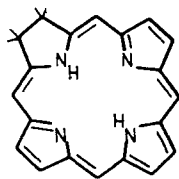
A. GENERAL REMARKS

An increasing number of porphinoid macrocyclic pigments have been found to be related to important biochemical processes. As a result, much of the pertinent chemistry has been thoroughly studied.

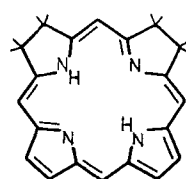
Early investigations of photosynthesis in bacteria and plants have led to a study of chlorins II. Quite recently the problem of biosynthesis of vitamin B₁₂ has been shown to be connected to chlorins II, isobacteriochlorins III, and pyrrocorphins V.



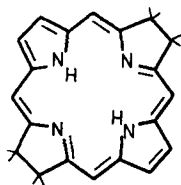
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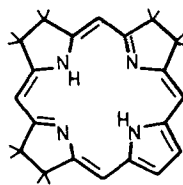
II



III



IV



V

These and other biochemical implications of hydroporphyrins are portrayed in Section V.

Hydroporphyrins may also answer theoretical questions. Porphyrin(I) is generally regarded as a very stable aromatic system. A convincing explanation of its aromaticity has been given (86PAC67). Several publications deal with the question of the preferred path of delocalization, which is related to structure, reactivity, and tautomerism of porphyrins. The connection of this problem to the properties of hydroporphyrins is obvious. As a consequence, some aspects of porphyrin chemistry are included in this article.

The chemistry of porphyrins is well documented (75MI1) (78MI1) and chlorophylls (66MI1) as well as bacteriochlorophylls (78MI10) have been reviewed extensively. A review on hydroporphyrins (78MI3; 78MI4) comprises publications up to 1975. Since the field has expanded enormously since then, a new review seems appropriate. Subjects that were dealt with previously will be treated only briefly here unless there have been important new developments.

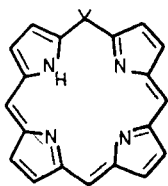
B. NOMENCLATURE

Nomenclature follows IUPAC recommendations (79PAC2251). The basic macrocyclic system I is named *porphyrin*, which implies that the "pyrrolic" nitrogen atoms are placed in positions-21 and -23, regardless of the structure of the actual tautomer. Hydro prefixes are then considered in ascending numerical order. I attempt here to maintain the arrangements of the formulas of hydroporphyrins resulting from these rules.

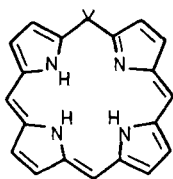
It is helpful to differentiate topologically peripheral positions (2, 3, 7, etc.) from meso positions (5, 10, 15, 20). Thus, two fundamental types of hydroporphyrins may be deduced.

Most common are derivatives hydrogenated at peripheral positions. They are named chlorins (II), isobacteriochlorins (III), bacteriochlorins (IV), and pyrrocorphins (V). These contain at least one cyclic conjugated system.

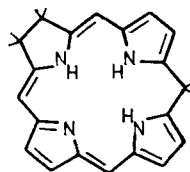
Saturation at a meso position, interrupting cyclic conjugation, is met with isoporphyrin (VI), phlorin (VII), β -chlorophlorin (VIII), porphodimethene (IX), porphomethene (X) and porphyrinogen (XI).



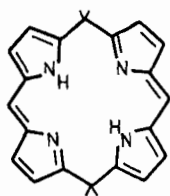
VI



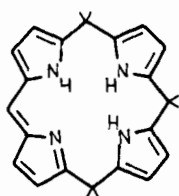
VII



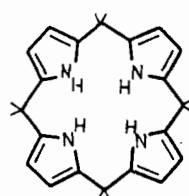
VIII



IX

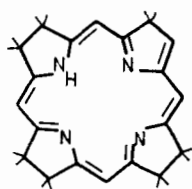


X

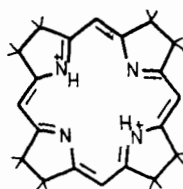


XI

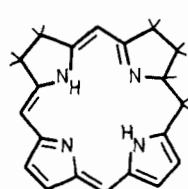
Numerous mixed types deriving from porphyrin by reduction at nitrogen atoms and peripheral as well as meso positions are conceivable. Derivatives XII–XVI of hydroporphyrins are covered in this article.



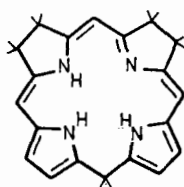
XII



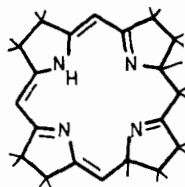
XIII



XIV



XV

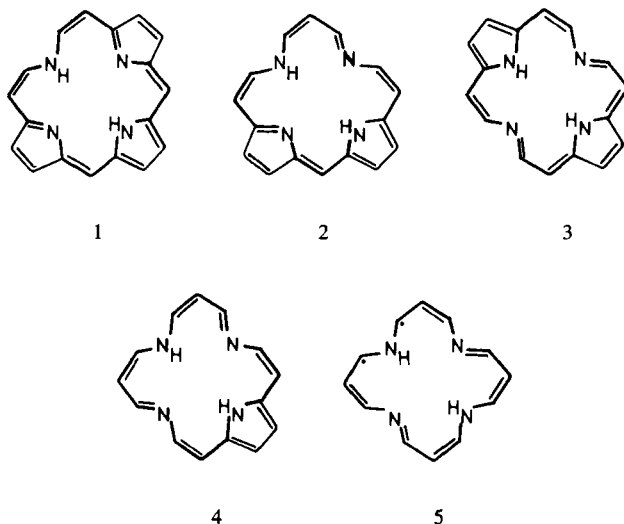


XVI

Corphin (XII) is cross-conjugated at C-9 and upon diprotonation is transformed into the conjugated dication XIII. The remaining π -systems show interrupted conjugation at least at one peripheral position.

In addition to hydroporphyrins, norporphyrins 1–5 will be considered; they are the cyclic conjugated parent compounds of peripherally saturated hydroporphyrins II–V (86PAC153).

Compounds containing an *extension* of the chlorophyll π -system have also been studied (78TL1043); these differ from the chemistry of hydroporphyrins described here (e.g., 138 in Section V).



C. ABBREVIATIONS

Abbreviations used in this article follow common practice pointing to substituents and the core of the molecule.

Substituents: OE(M) indicates octaethyl (methyl) groups in peripheral positions, TP(M) characterizes tetraphenyl (methyl) groups in meso positions.

Core abbreviations are: P = porphyrin (I), C = chlorin (II), iBC = isobacteriochlorin (III), BC = bacteriochlorin (IV), and Pc = pyrrocorphin (V).

The construction of abbreviations for a particular porphyrinoid (e.g., OEC or TMPC) is self-evident.

II. Structure

A. THEORETICAL CHEMISTRY

Norporphyrins 1–4 and hydroporphyrins II–V all represent types of 18 π -electron conjugation pathways in porphyrins (75CRV85). The properties of these compounds may therefore reflect the importance of a particular path of delocalization in a discussion of structure or reactivity. Even more important are differences of particular hydroporphyrins in view of many biochemical processes (81JA5890).

Molecular orbital (MO) calculations of porphyrins have been reviewed (78M17) and a simple PMO model was described (86PAC153). HMO

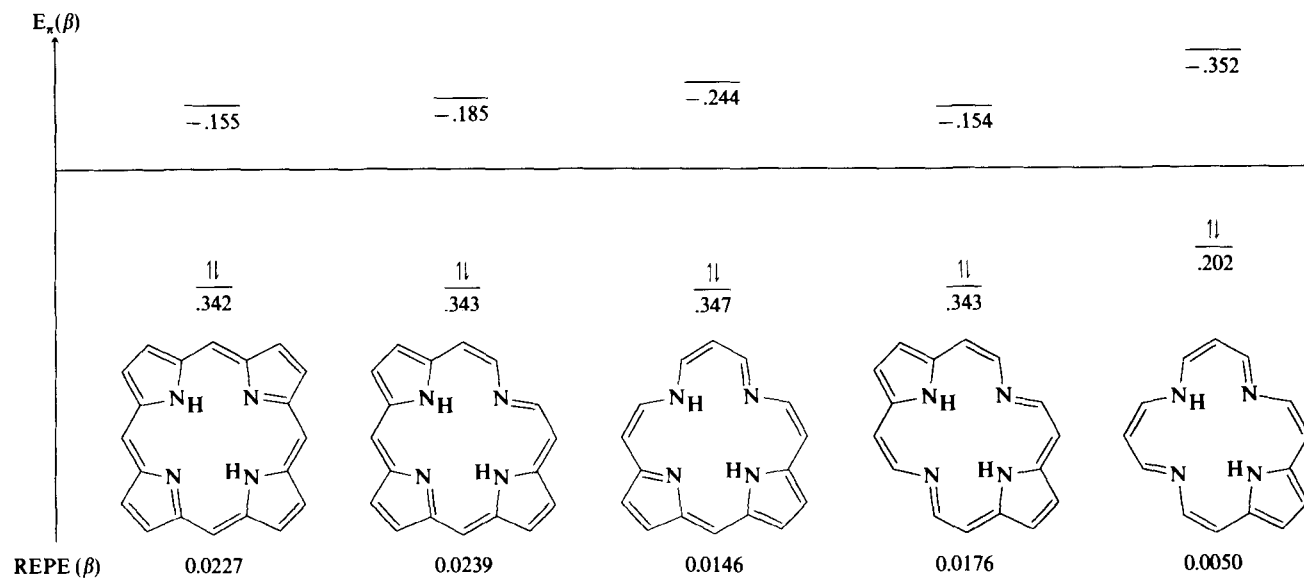
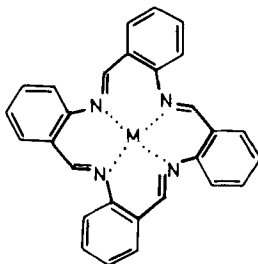


FIG. 1. Eigenvalues of frontier orbitals of the most stable tautomers of porphyrin and norporphyrins.

eigenvalues of frontier orbitals and resonance energy (REPE) values of porphyrin (**1**) and norporphyrins (**1**–**5**) are presented in Fig. 1 (86UP1). Eigenvectors of porphyrin were used together with conventional reactivity indices for a rationalization of reactivity phenomena (75MI5; 78MI6).

Several conclusions may be drawn from Fig. 1. Taking away one or two double bonds from porphyrin (**1**) does not change the resonance energy significantly. There is, however, a topological control on the separation of the second double bond; the REPE value of isobacteriophin **2** is substantially smaller than that of the isomeric bacteriophin **3**. A poor stability and a high propensity to oxidation may be deduced from the eigenvalue of the highest occupied molecular orbital (HOMO) and the REPE value of pyrrophin **4**; this agrees with evidence given in Section VI. The open-shell system **5** is expected to be extremely unstable.

Dehydro derivatives of **5** have been obtained only as metal complexes with peculiar properties. Thus, metal complexes of **6** are easily accessible from *o*-aminobenzaldehyde, but numerous attempts to remove the metal from **6** have only led to rearranged products (82CC17).



6

Just as with porphyrins (75MI2; 78MI2), the properties of hydroporphyrins are greatly affected by metallation. Metal–ligand interactions have been treated by crystal field theory (electrostatic) or by using perturbation theory. A report of preliminary studies of Fe(II) complexes with unsaturated ligands, especially porphyrin, has been given based on the concept of cruciaromaticity (86PAC67), which may be helpful for a rationalization of experimental findings.

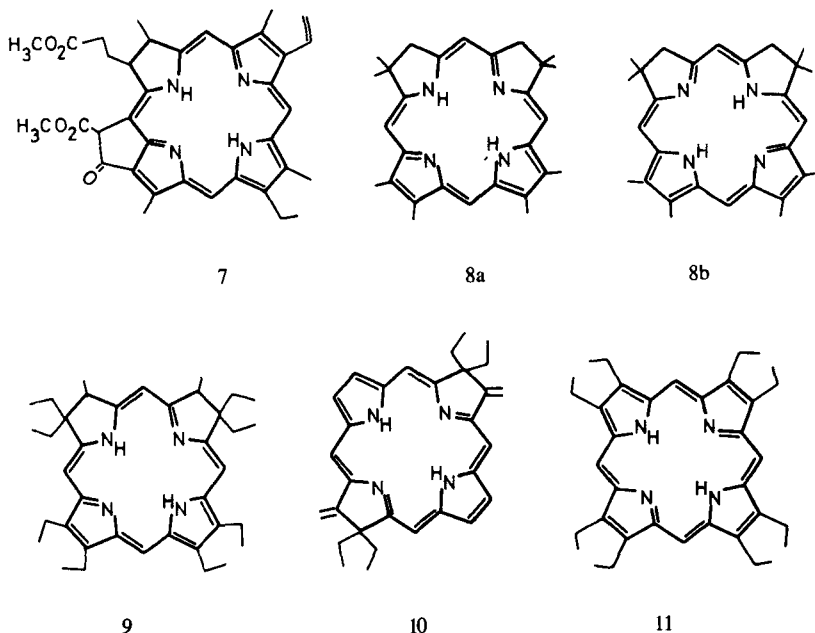
B. MOLECULAR STRUCTURE

X-Ray structure determinations of porphyrins have been reviewed (75MI3; 78MI9). Selected data of porphyrins and hydroporphyrins are given in Table I.

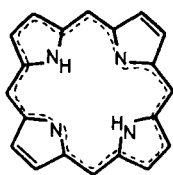
TABLE I
BOND DISTANCES (Å) IN PORPHYRINS AND HYDROPORPHYRINS

	I	II	7	8	9	10
C _α —N	1.37–1.38	1.36–1.37	1.30–1.39	1.33–1.39	1.34–1.41	1.35–1.37
C _α —C _β	1.43–1.45	1.44–1.46	1.39–1.46	1.42–1.44	1.41–1.44	1.43
C _α —C _m	1.38	1.39	1.37–1.41	1.36–1.38	1.39–1.44	1.39
C _β —C _β	1.34–1.36	1.35–1.37	1.35–1.46	1.36–1.37	1.34–1.36	1.37
Reference	[72JA4144]	[73JA5148]	[72JA3613]	[82JA2376]	[82JA315]	[84JA6457]

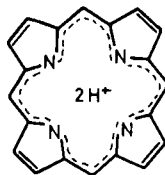
Generally, the chromophore of porphyrins and hydroporphyrins tends to be planar, deviations being more facile in hydroporphyrins owing to their decreased aromaticity. A comparison of the planar isobacteriochlorin **8** with the nonplanar derivative **9** illustrates that steric interactions of β -substituents may give rise to distortions.



Planar hydroporphyrins have intrinsically larger cores (i.e., distances between opposite nitrogen atoms) than porphyrins. Deviation from planarity leads to a reduction in core size. As a result, the energy barrier for contraction of the macrocyclic core of hydroporphyrins upon complexation to small metals (e.g., Ni(II) or low- or intermediate-spin Fe(III)) is small. Experimental results have been discussed in detail (85JA4207).



XVII



XVIII

Two proposals for the aromatic delocalization pathway of porphyrins have been considered; these are represented here by **XVII** and **XVIII**. In structure **XVII**, there is an 18-atom conjugation pathway, with the additional possibility of two or more tautomeric forms governed by the positions of the internal hydrogens. Structure **XVIII** features a 16-atom dianion pathway, the bonding of the internal hydrogens to nitrogen being ionic or dative. The last mentioned proposal was derived from X-ray data, which showed the pyrrole rings to be essentially equivalent with the $C_\beta-C_\beta$ bonds as almost pure double bonds. The two central hydrogen atoms were not localized (70AC(R)105).

More recent X-ray studies, however, have shown the two central hydrogen atoms of porphyrins (75MI3; 78M18) and hydroporphyrins bonded to opposite nitrogen atoms. Moreover, rings containing NH groups differ structurally from the other rings. Hydrogen atoms attached to adjacent nitrogen atoms are sufficiently close to cause the entire chromophore to be considerably buckled.

The isobacteriochlorin **8** serves as an example. Two protons distributed between the four nitrogen atoms with a 50% occupancy at each site were found experimentally. It has been suggested that two tautomeric forms (**8a**, **b**) contribute, equally to the solid-state structure. Two $C_\alpha-N$ bonds ($\Delta = 0.051 \text{ \AA}$) and two $C_\alpha-C_m$ bonds ($\Delta = 0.077 \text{ \AA}$) are significantly different as a result of the superposition of the tautomeric forms (82JA2376).

Table reveals no major variation of bond distances on progressive saturation of the porphyrin macrocycle.

Given that all structurally characterized Ni(II) and Fe(II) hydroporphyrins are distorted while both planar and distorted porphyrins are known, two points have been made: (1) hydroporphyrins distort more easily than porphyrins; (2) the energy barrier for contraction of the macrocyclic core (with resulting nonplanarity) upon complexation to small metals is low (85JA4207).

The greater structure compliance of hydroporphyrins over porphyrins may be a factor of chemical and biological significance (83JA4108).

Porphyrins and hydroporphyrins show molecular packing in which a ring of one molecule overlaps with that of a second molecule with a vertical

separation indicative of $[\pi-\pi]$ -interactions. A mechanism is thus provided for exciton migration in the crystal similar to those observed *in vivo* (84JA6457).

C. MOLECULAR SPECTRA

1. Ultraviolet and Visible Spectra

Facts on optical absorption and emission spectra of porphyrins and porphyrinoids, together with the molecular orbital theory by which these are understood, have been described by M. Gouterman (78MI7). Molecular orbital theory has proved extremely useful for a rationalization of the relationship between structure and optical spectra. The field has been reviewed (72JSP37). The Hückel model can be used to get a qualitative idea of how a diminution of the porphyrin π -system can effect transitions. The successful four-orbital model of Gouterman explains the bathochromic shift and the intensification of the Q -band upon reduction, as well as differences between bacteriochlorin and isobacteriochlorin spectra. Some PPP calculations include extensive configuration interactions (CI) among all excited states (72ZN(A)1663). Generalizations, especially those concerning hydroporphyrins, include the following.

(1) Porphyrins show a four-band, and metalloporphyrins a two-band, visible spectrum. The difference arises from the fact that the two free-base hydrogens in the center strongly reduce the conjugated ring symmetry from square (D_{4h}) to rectangular (D_{2h}). Change from the base to metal complexes has a less dramatic effect on the spectra of hydroporphyrins, because ring reduction has already lifted the degeneration of the square ring.

2. Reduction of the porphyrin π -system results in a bathochromic shift and an enhancement of the extinction coefficient of the Q -band. There are characteristic differences between bacteriochlorins and isobacteriochlorins. An ultraviolet spectrum of a pyrrocorphin (15) has been described, proving earlier reports on a synthesis of this compound to be erroneous (85CC1604).

3. There are reasons for a substantially higher fluorescence yield in hydroporphyrins than in porphyrins (78MI7).

4. The electronic states of hydroporphyrins are to the red of porphyrins. As a result, phosphorescence shifts to the red and the triplet lifetime and triplet yield decrease (78MI7).

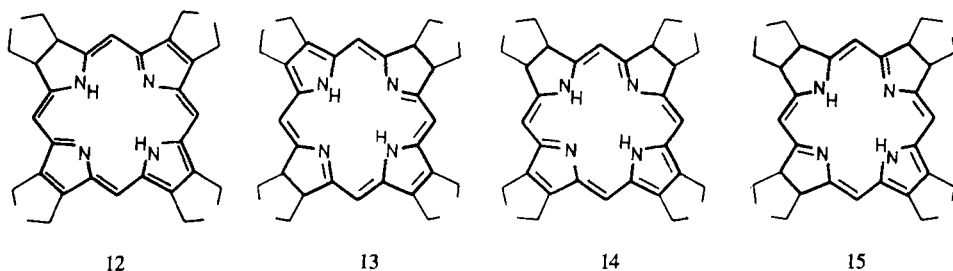
5. UV spectra of the norporphyrins 2 and 3 are very similar to those of OEiBC(14) and OEBC(13). A hypsochromic shift of 2 and 3 points to a deviation from planarity in the hydroporphyrins (86PAC153). Similar steric interactions of substituents at the saturated bridge of hydroporphyrins have been observed in OEC (69TL1145).

Some of these rules are illustrated in Table II.

TABLE II
UV SPECTRA OF HYDROPORPHYRINS

Solvents			Soret region						
11	Benzene	(57JCS733)	400(5.20)	498(4.02)	542(4.09), 568(3.83), 596(3.18), 622(3.76)				
12	Cyclohexane	(69TL1145)	380(4.98)						
	<i>cis</i>		392.5(5.24)	497(4.13)				651(4.94)	
	<i>trans</i>		390.5(5.29)	496.5(4.10)				646.5(5.02)	
13	Benzene	(57JCS3461)	374(5.26)	434(3.96), 463(4.31), 491(4.69)			604(3.39), 661.5(3.89), 685(4.15), 721(5.18)		
14	Benzene	(80JA364)	355(s, 4.69) 370(4.94)	380(4.89) 402(4.05)	480(3.74)	510(3.93)	545(4.18)	586(4.44)	635(3.92)
15	Benzene	(85CC1604)	326(s, 4.69) 341(s, 4.80) 347(4.81)	379(4.64)	443(s, 3.66)	470(s, 3.93)	503(4.10)	546(4.11)	592(4.17)
3 ^a	CHCl ₃	(86PAC153)	332(0.54)	350(i.o.)	433(0.04), 463(0.05), 491(0.31)		562(<0.05), 628(0.03), 641(0.05), 671(0.74)		
2	CHCl ₃	(86PAC153)	262(3.84) 352(s, 433)	370(4.56)	458(3.26)	490(3.53)	527(3.71)	566(3.76)	612(2.78)

^a (Relative intensities).



2. Infrared Spectra

Evidence of tautomerism of isobacteriochlorins has been found in infrared (IR) spectra. In contrast to porphyrins and chlorins, which have only one NH stretching frequency, bacteriochlorins exhibit two peaks (79AG(E)675). These may either result from two nonequivalent trans-positioned nitrogens or reflect the presence of both cis and trans tautomers. The energy difference ($\nu_{\text{NH}} \approx 100 \text{ cm}^{-1}$) has been thought to be too large for two different NH groups. Moreover, the ratio of the two bands is temperature dependent, the intensity of the lower frequency band increasing at elevated temperature. As a consequence, more of the cis tautomer would be formed as the temperature increases. This assignment, however, is only tentative and more data are needed to be definitive (80B1971).

Iron chlorin complexes have been studied by resonance Raman spectroscopy. Observations have predictive value, and offer criteria for an identification of metallochlorin prosthetic groups in biological systems (85JA182).

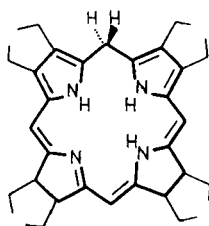
3. NMR Spectra

a. *¹H-NMR Spectra.* ¹H-NMR spectra of porphyrins and hydroporphyrins have been reviewed (75MI4; 79MI1; 79MI2) and a series is forthcoming (28. communication: (86JA1111)). Porphyrins I and hydroporphyrins II–V comprise a conjugated macrocycle and are diatropic (i.e., protons outside the ring resonate at lower field than protons not influenced by the ring current, whereas protons inside the ring occur at higher field). Examples in Table III illustrate this; 16 may be taken as a reference compound, since conjugation is interrupted here.

Removal of peripheral double bonds leads to a decrease in ring current. This is moderate in chlorins (II) and bacteriochlorins (IV) and substantial in isobacteriochlorins (III). Pyrrocorphins (V) are nearly anisotropic compounds (compare 15 with 16 in Table III). ¹H-NMR studies of *meso*-

TABLE III
¹H-NMR SPECTRA OF HYDROPORPHYRINS

	$\delta_{\text{meso-CH}}$	δ_{NH}	Solvent	References
11	10.18	- 3.74	CDCl ₃	[66LA(695)133]
12	9.71,8.87	- 2.51	CDCl ₃	[80JA364]
<i>cis</i>	9.87,8.91	- 1.84	C ₆ D ₆	[69TL1145]
<i>trans</i>	9.75,8.79	- 1.69	Cl ₃	
13	8.82	- 1.88	C ₆ D ₆	[69TL1145]
14	8.52/8.50(1h)	2.98	CDCl ₃	
	7.47/7.45(2h)			
	5.88/6.86(1h)			[80JA364]
	8.78/8.75(1h)	3.65	C ₆ D ₆	[80AG(E)140]
	7.64/7.62(2h)			
	6.85/6.76(1h)			
15	6.02,6.60	5.74	CS ₂ /CD ₂ Cl ₂	[85CC1604]
16	5.00/5.05	7.92	CDCl ₃	[80AG(E)140]
	6.61/6.64			
3	9.10	- 3.72	CDCl ₃	[86PAC153]
2	8.84	2.30,2.00	CDCl ₃	
	$\delta_{\beta\text{-Pyrrolo, CH}_2}$			
Ni(II)-TMP	9.23		CDCl ₃	[82JHC413]
Ni(II)-(TMC)	8.65,8.46		CDCl ₃	[82JHC413]
Ni(II)-(TMiBC)	8.14,7.61		CDCl ₃	[84JA5164]



16

tetraphenylporphyrins (810MR1) and other hydroporphyrins confirmed the order porphyrin (I) > chlorin (II) ≥ bacteriochlorin (IV) >> isobacteriochlorin (III) >> pyrrcorphin (V) of diatropicity, which may also hold for norporphins (86PAC153) and metal complexes of hydroporphyrins (see Table III).

Torsional influences on ring current may be deduced from a comparison of *cis*- and *trans*-OEC (12) (69TL1145). A ring current model for chlorophyll derivatives has been described (82JA4332).

In addition to X-ray studies (Section II.B), ^1H -NMR investigations revealed that the central hydrogens of porphyrins and hydroporphyrins are bonded to opposite nitrogen atoms: Two distinct types of β -pyrrolic protons in TPP at -80°C and two NH signals in chlorine e_6 trimethyl ester at 10°C were observed (72JA1745). From NMR evidence, OEiBC (**14**) is most probably a mixture of two nearly equally abundant isomers with opposite NH-groups (80JA364). Even in the norporphins **2** and **3**, NH protons seem to be in a trans position (86PAC153). Splitting of NH signals in **2**, which is also typical for chlorins and particularly phorbins, is indicative of a pronounced localization of NH protons in hydroporphyrins as compared with porphyrins (66LA(695)112).

Apparently the stability of hydroporphyrin tautomers is governed by two structural features: (1) Protons at adjacent nitrogen atoms give rise to steric strain. Therefore, the tautomer with protons at opposite nitrogen atoms will be more stable. (2) Protons will try to avoid positions at nitrogen atoms of hydrogenated pyrroline rings, thus enabling a more effective conjugation via a pyridine-type nitrogen atom.

An analysis of variable-temperature ^1H -NMR spectra showed that Fe(II)-OEC possesses rhombic magnetic anisotropy (85JA4207).

b. ^{13}C -NMR Spectra. ^1H -NMR studies are frequently complicated somewhat by the dependence of chemical shifts on aggregation and solvation. This complication is not expected to arise with ^{13}C -NMR studies because chemical shifts in this case are largely determined by paramagnetic screening terms (70AC(R)105). Evidence was presented for a preferred delocalization pathway in porphyrins corresponding to structure XVIII (72JA2510). The conclusions of this work, however, have been questioned, and the experiments shown to favor XVII (74JCS(P2)627).

c. ^{15}N -NMR Spectra. ^{15}N -NMR has been used to study localization and transfer of NH protons in porphyrins (84JA292; 84JA4059).

D. MISCELLANEOUS PHYSICAL METHODS

A compilation of mass spectra of hydroporphins has been given (78MI8).

Magnetic circular dichroism (MCD) spectra of a number of unsubstituted, alkyl-substituted, and tetraphenyl-substituted hydroporphyrins have been used for new assignments for the location of the Q_0 transition (82JA4305). The data were subjected to a PMO analysis using a protocol which does not require explicit numerical calculations. In conjunction with Michl's perimeter

model MCD band sign patterns of porphyrins and hydroporphyrins were correctly described. The model may be a useful first-order structure elucidation technique for other systems (82JA4317).

III. Reactions

Reactions used to transform hydroporphyrins into porphyrinoids of different conjugation pattern are covered in Section IV.

A. BASICITY

The relative basicities of hydroporphyrins as inversely related to the strength of phosphoric acid needed to extract them from benzene solution are: TPP > TPC \cong TPiBC > TPBC (69JA7485).

Protonation of hydroporphyrins yields diacids, which, similar to diacids of porphyrins (70AC(R)105), are highly nonplanar because of van der Waals and Coulomb repulsions of the four inner hydrogen atoms.

B. TAUTOMERISM

Tautomerism of *meso*-hydroxyporphyrins has been reviewed (78MI4). Interconversions of tautomeric hydroporphyrins are described in Section IV,B. The stereoselectivity of the corphin-pyrrocorphin tautomerization (XII \rightleftharpoons V) has been studied (83AG(E)630).

C. SUBSTITUTION REACTIONS

Chlorination, bromination, and nitration of chlorins occur preferentially at *meso*-positions adjacent to the hydrogenated pyrroline ring (65JOC2791; 66JCS(C)1600).

Deuteration of hydroporphyrins in dideuteriosulfuric acid has been studied. The rates increase in the sequence OEP (**11**) \leq 5,20-OEC (**12**) (trans isomer) \leq 10,15-OEC (**12**) < **15**-OEiBC (**14**) (mixture of isomers) < 10,20-OEiBC (**14**).

A correlation between observed reactivity and calculated π -density has been stated (67JCS(C)1168). The directing influence of the hydrogenated pyrroline rings in **12** and **14** seems noteworthy.

Meso substitution of chlorins has been used to transform bacteriopheophorbides *d* into bacteriopheophorbides *c* (85JA4946).

Smith and co-workers have shown that the π -radical cation produced by oxidation of metallochlorins (and metalloporphyrins) can undergo meso substitution with various nucleophiles (79JA5953).

D. OXIDATION AND REDUCTION

Synthetic aspects are treated in Sections IV,A (reduction) and IV,C (oxidation). Redox reactions of porphyrins useful for hydroporphyrins have also been described by Fuhrhop (75MI5).

Three regularities in potentials have been observed and serve as criteria for ligand-based oxidation and reduction.

1. The difference between the first one-electron oxidation and reduction potential is 2.25 ± 0.2 V.
2. The second removal or addition of an electron follows after an interval of 0.2–0.4 V.
3. Reduction of a peripheral double bond lowers the oxidation potential by about 0.2–0.3 V.

These regularities are effective also in metal complexes. Electronegativity of metals may strongly affect individual potentials, however.

Table IV illustrates these rules, which are overridden by electron-attracting substituents, as was shown for oxochlorins (86JA1352).

Facile oxidation of isobacteriochlorins compared to porphyrins and chlorins has been stated. Extended Hückel calculations helped to rationalize these differences, indicating likewise that Fe(II) pyridine carbonyl complexes of isobacteriochlorins, unlike those of porphyrins and chlorins, undergo oxidation from the macrocycle rather than the metal to form π radical cations (81PNA2652).

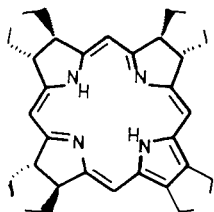
TABLE IV
REDOX POTENTIALS OF HYDROPORPHYRIN^a

	Solvent	$2^+/1^+$	$1^+/0$	$0/1^-$	$1^-/2^-$
11	<i>n</i> -C ₃ H ₇ CN	+1.40	+0.89	-1.44	-1.30
12	<i>n</i> -C ₃ H ₇ CN	+1.18	+0.64	-1.47	-1.95
	CH ₃ CN	+1.11	+0.59	-1.46	~ -1.9
	CH ₃ CN				
14	CH ₃ CN	+0.88	+0.34	-1.70	—
(Fe-OEP)Cl	CH ₂ Cl ₂	+1.39	+1.01	-0.52	—
(Fe-OEC)Cl	CH ₂ Cl ₂	+1.24	+0.72	-0.44	—
(Fe-OEtBC)Cl	CH ₂ Cl ₂	+1.00	+0.43	-0.45	—

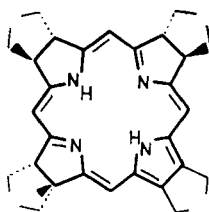
^a (80JA364), (81JA4763).

E. MISCELLANEOUS REACTIONS

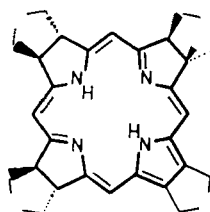
In the context of a chemical study related to problems of vitamin B₁₂ biosynthesis, peripheral C-methylation of the magnesium complex of tctct-OEPc (17) was reported to yield a mixture of isomeric products (18a–c) (83AG(E)631). A similar reaction was found to occur at C-12 of nonamethyl pyrrocorphin (19). One of the by-products of this reaction is the seco-corphinoid derivative 20, which, on complexation with Ni(II) acetate, cyclizes to give an Ni(II) corrinate (21) (84CC583).



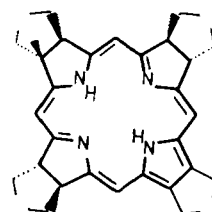
17



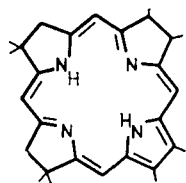
18a



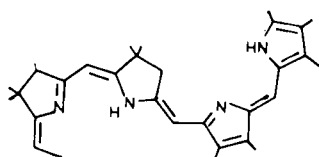
18b



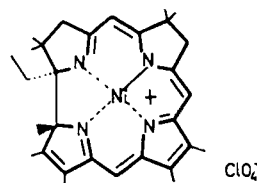
18c



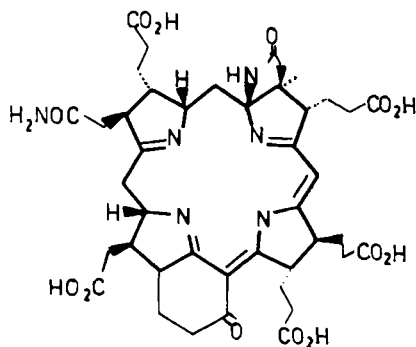
19



20



21



22

Thermal isomerization of factor F430 (**22**) led to an equilibrium mixture of three epimers, differing in configuration at C-12 and C-13. Two of the epimers are isolated artifacts described earlier in the literature (85HCA1338).

IV. Syntheses

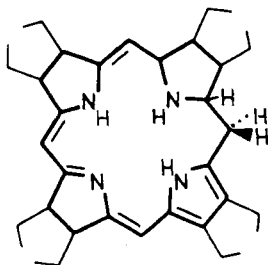
A. REDUCTION OF PORPHYRINS AND HYDROPORPHYRINS

Reduction may occur at peripheral or at meso positions of porphyrins and subsequent rearrangement can occur (see Section IV,B). Since experiments concerning this matter are scarce, the classification given here is based on reagents rather than on mechanistic arguments.

1. Reduction by Metals

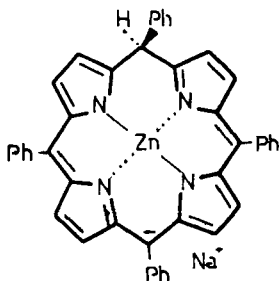
a. *Sodium and Alcohols.* This method was first used by H. Fischer *et al.* to reduce Fe complexes of aethioporphyrin (30LA(479)40). The corresponding chlorin was found together with a red perhydro derivative, which was dehydrogenated to the chlorin. These results were confirmed 20 years later. A pure tetrahydroaethioporphyrin was obtained by chromatography and characterized by quantitative dehydrogenation to aethiochlorin. Neither analytical nor spectral data were recorded (50JA2867).

In a painstaking investigation, U. Eisner (57JCS3461) showed that reaction of OEP (**11**) with sodium and isopentyl alcohol gives OEC (**12**), OEiBC (**14**), and traces of OEBC (**13**) [see also (67JCS(C)1168)]. A similar reduction of OEC (**12**) afforded, in addition to the tetrahydro derivatives **13** and **14**, a hexahydro derivative, which was thought to be OEPc (**15**) but later shown to be a mixture of four diastereomeric porphyrinoids **23** with interrupted conjugation (80AG(E)141).

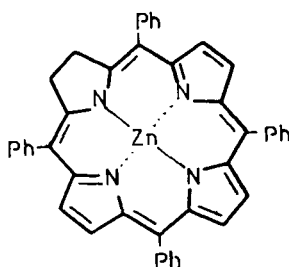


The products of reduction of OEP (**11**) with sodium and alcohol are *trans*-OEC (**12**) (69TL1141) and a mixture of four diastereomeric OEiBC's (**14**) (80AG(E)141). The reduction of porphyrin complexes as well as tautomerization of porphyrinogens (Section IV,B) preferentially yield hydroporphyrins, which are abundant in nature. Considering, for example, sirohydrochlorin (Section V), it is interesting to note that the only tetrahydroporphyrins formed in substantial yield during the above-mentioned reactions are of isobacteriochlorin type **III**. A short bibliography has been given (80AG(E)141).

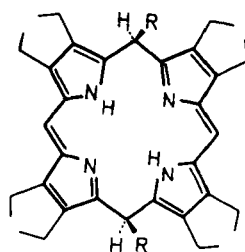
b. *Reductions via Radical Anions.* Zn-TPP has been transformed into a radical anion with sodium benzophenone ketyl in tetrahydrofuran. A dianion is formed with the anion of anthracene. Protonation with methanol gave the phlorin zinc complex **24**, which rearranged slowly to Zn-TPc (**25**) (63JA818). The dianion of Zn-TPP was alkylated at the meso positions, yielding, after decomplexation, *cis*-5,15-dialkylporphodimethenes (**26**), whose configuration has been discussed (84LA1259). A similar mechanism for reduction of porphyrins by sodium and alcohol (cf. preceding section) seems to be a reasonable assumption.



24



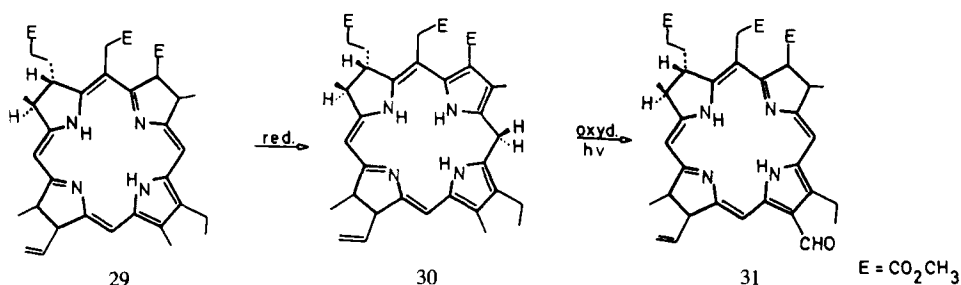
25



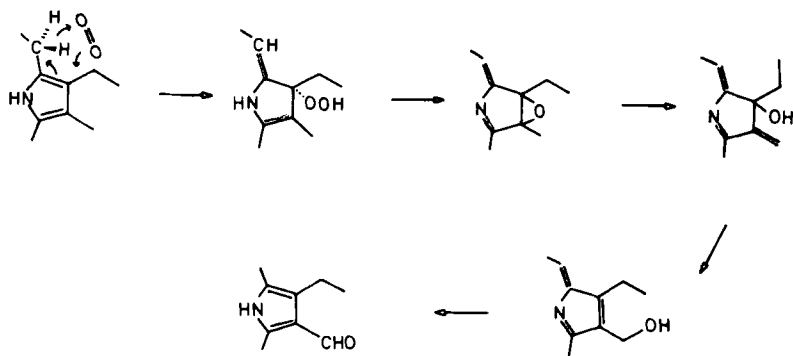
26

2. Electrochemical Reductions

Electrochemical reductions of porphyrins (60MI1; 64TL1317) and chlorins (65TL3387; 66TL4283) have been described. One-electron reduction normally affords isomeric but less stable phlorins (**VII**). The most surprising synthetic application of electrolysis of chlorins is the successful conversion of chlorin *e*₆ trimethyl ester **29** (Scheme I) into rhodin *g*₇ trimethyl ester (**30**), achieved by Inhoffen (67LA(704)188; 71LA(749)109). Compound **29** was transformed into the chlorin- β -phlorin (**30**) electrochemically in almost quantitative yield. A



Mechanism:



SCHEME 1

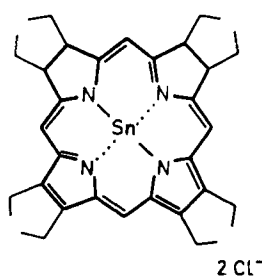
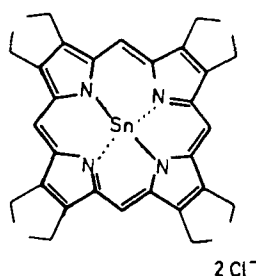
subsequent photochemical oxidation changed a peripheral methyl group into an aldehyde function, as indicated in Scheme 1.

Redox properties of hydroporphyrins are treated in Section III,D.

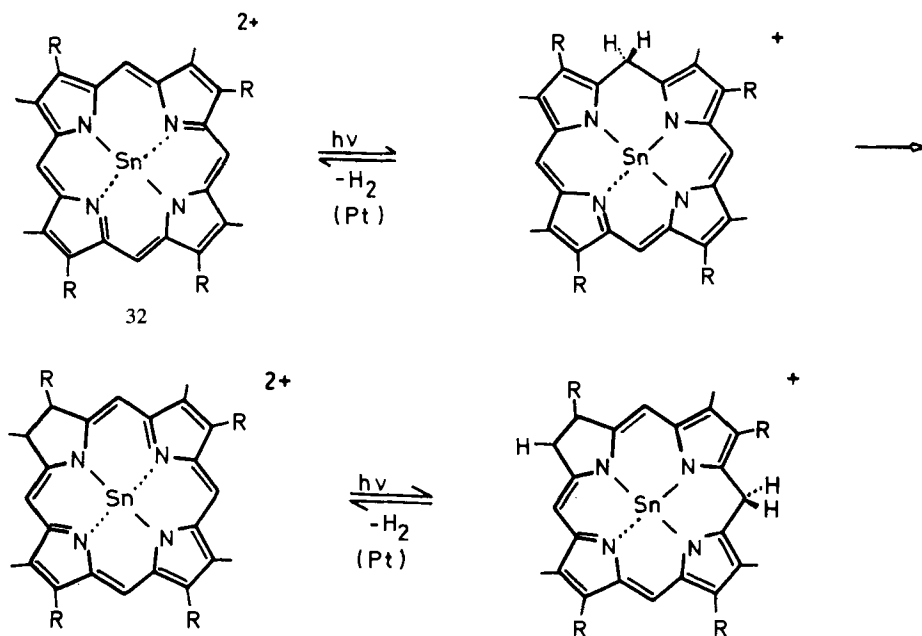
3. Photochemical Reductions

Photoreductions of free base porphyrins and metal complexes with a variety of reducing agents, including ascorbic acid, glutathione, ethylenediaminetetraacetic acid (EDTA), and acetoacetate, have been studied mainly from a mechanistic point of view (75MI6). Unstable hydroporphyrins of phlorin type VI are formed, which subsequently isomerize to chlorins, bacteriochlorins, or isobacteriochlorins.

Preparative aspects have only rarely been regarded. The conversion of Sn(IV)-OEP (27) into the corresponding isobacteriochlorin complex 28 is nearly quantitative without formation of the bacteriochlorin isomer (71JA2291).



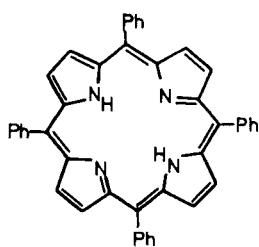
From a photochemical reduction of the water-soluble porphyrin **32**, hydrogen was obtained in a reaction sequence (Scheme 2) simulating the biosynthesis of chlorophyll as well as the hydrogen formation in photosynthesis (82AG132).



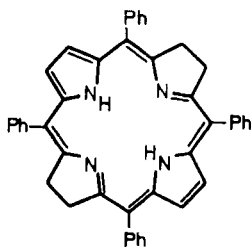
SCHEME 2

4. Catalytic Hydrogenation

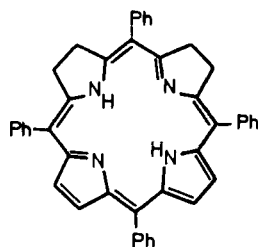
Peripheral double bonds of porphyrins and hydroporphyrins may be hydrogenated catalytically. Zn-OEP on treatment with hydrogen at 180 and 90°C in dioxane solution gave 8% *cis*-OEC (12) after demetallation (69TL1145). Low yields of TPBC (34) and TPiBC (35) were obtained from a Raney nickel reduction of TPP (33) in ether and dioxane, respectively. Tetrahydroporphyrins, however, were not isolated, and characterized only on the basis of their optical spectra (52JA6101).



33



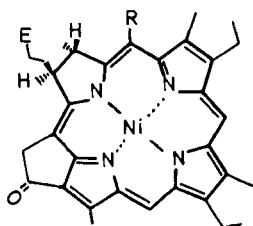
34



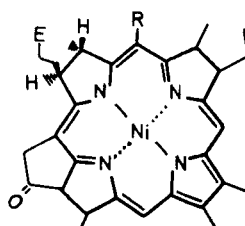
35

A reduction of chlorophyll derivative **36a** with Raney nickel gave the isobacteriochlorin **37a** and the pyrocorphin **38a**. A similar reduction of **36b** led to **36c**, **37b**, and **38b**. The nickel isobacteriochlorin **37** was shown to consist substantially of one isomer (tcc) by high-performance liquid chromatography (HPLC) and NMR spectroscopy. As a consequence of the presence of the meso substituent in **36b**, a significantly higher yield of the isobacteriochlorin **37b** was obtained as compared with the reduction of **36a** to give **37a** (85JA4954).

Catalytic hydrogenation of the isobacteriochlorin **39** carried out with Pt/C in ethyl acetate at ambient temperature occurred at the meso position, yielding phlorin-type **40**, which subsequently was isomerized to **41** in formic acid at 70°C (80AG(E)143).

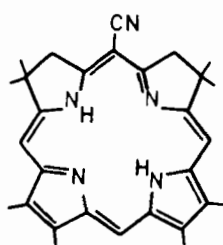
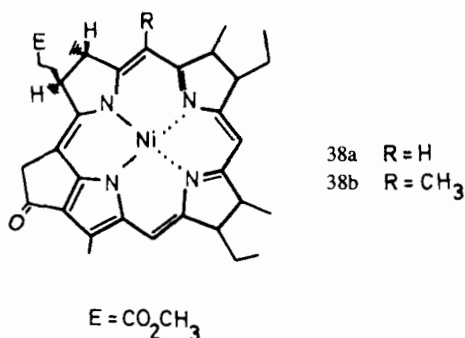


36a R = H

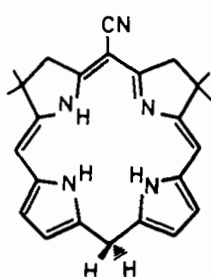
36b R = CH₂SCH₃36c R = CH₃

37a R = H

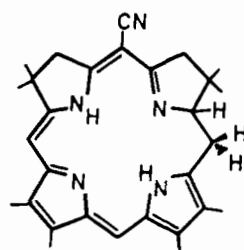
37b R = CH₃E = CO₂CH₃



39



40

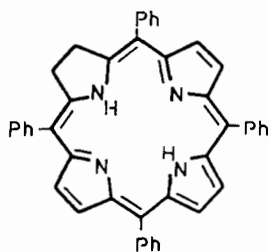


41

5. Miscellaneous Reductions

Hydroboration of Zn-OEP gave a 5:1 mixture of *cis*- and *trans*-OEC (**12**), indicating two competing reductions in which the *trans* isomer is formed via a phlorin intermediate, rather than by direct attack of the boron hydride at the peripheral double bond (69TL1145).

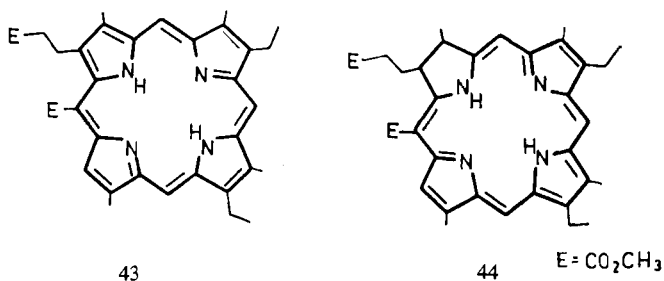
Diimide reduction of TPP (**33**) led to TPC (**42**) and TPBC (**34**), contaminated by no more than 2–4% of TPiBC (**35**). A remarkable feature is the influence of chelated zinc on the regioselectivity of this reaction. Zn-TPC (**25**)



42

affords Zn-TPiBC (**35**) with a similar degree of selectivity. The reductions have been shown to underlie kinetic control. OEP (**11**) was transformed into OEC (**12**) (69JA7485).

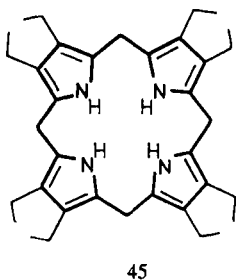
A 20% transformation of the phylloporphyrin **43** into the chlorin **44** with sodium ethoxide at 185°C was reported (29LA(471)146). The structure of **44** was proved correct by X-ray crystallography (69MI1). Obviously, a steric interaction between peripheral substituents causes the driving force for the reaction, which otherwise is difficult to understand.



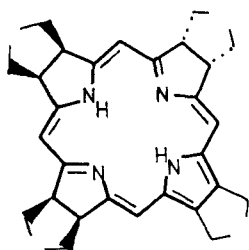
B. HYDROPORPHYRINS BY REARRANGEMENT

As shown in Section IV,A,1, reduction of porphyrins by electron-transfer reactions may proceed via intermediates with interrupted conjugation, which subsequently rearrange to hydroporphyrins, thus reestablishing cyclic conjugation. Interruption of conjugation can also be achieved by catalytic hydrogenation of hydroporphyrins (Section IV,A,4).

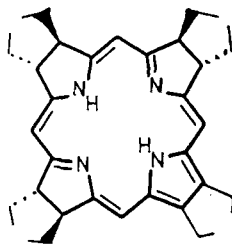
Metal complexes of porphyrinogens (**XI**), which are easily accessible by various routes (78MI15), are unstable. Rearrangements were studied carefully, mainly by the Eschenmoser group. Some examples may illustrate this. Tautomerization of octaethylporphyrinogen (**45**) on complexation with the Mg salt of 1,5,7-triazabicyclo[4.4.0]dec-5-ene, followed by decomplexation



with acetic acid, gave a mixture of OEPC's. Optical spectra and HPLC showed the composition to be mainly the ccctc isomer **46**, together with 11 of 20 possible diastereomers. Equilibration of this mixture gave three diastereomers containing only *trans* ethyl groups in vicinal positions. Pure crystalline tctct isomer **47** was obtained (83AG(E)630).

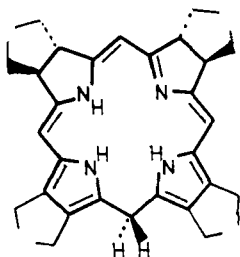


46

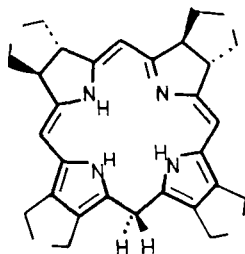


47

From a reaction of the porphyrinogen **45** with CoCl_2 , acetic acid, and triethylamine 19% *trans*-OEC (**12**), 10% *cis*-OEC (**12**), and a mixture of OEiBC's (**14**), mainly the tct and ttt isomers, were obtained after acidic demetallation. Catalytic hydrogenation of **14** led to isobacteriochlorin-phlorins **48** and **49**, which in pyridine/acetic acid gave **45** (80AG(E)140). Generally, in an equilibrium between porphyrinogens **XI** and isobacteriochlorin-phlorins **XV**, the former product is strongly favored but metal complexation may reverse this.



48



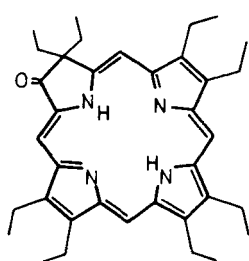
49

Strong control of rearrangements of porphyrinogens by metal complexation follows from a comparison of the reaction of **45** with CoCl_2 and NiCl_2 , respectively. Ni complexes **50** of hemicorrinoid-pyrromethenic character were formed in the latter reaction in up to 90% yield. Dehydrogenation of **50** gave the corresponding Ni-OEiBC's (80AG(E)141).

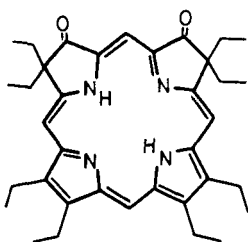
A crucial step in Woodward's approach to chlorophyll *a* (60AG651; 61PAC383) was the isomerization of porphyrin **51** into chlorin **52**. It is

An alternative approach to β,β' -dihydroxyhydroporphyrins is by treatment with OsO_4 . Glycols **53** are usually isolated before being rearranged to oxohydroporphyrins (69LA(725)167).

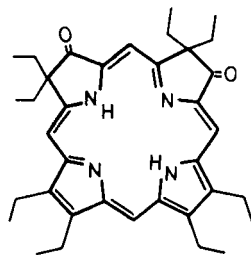
A painstaking investigation of the $\text{H}_2\text{O}_2/\text{H}_2\text{SO}_4$ oxidation of OEP (**11**) revealed the formation of the oxochlorin **54**, three dioxoisobacteriochlorins (**55** and **57**), two dioxobacteriochlorins (**58** and **59**), and two trioxopyrrocorphins (**60**–**61**). Trioxo derivatives **60** and **61** were obtained also from isobacteriochlorins **55** and **56** with OsO_4 via glycols and pinacol rearrangement. Interestingly, isomeric dioxobacteriophin **59** does not react with OsO_4 .



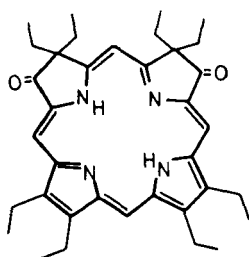
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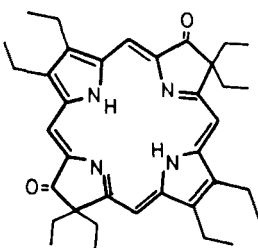
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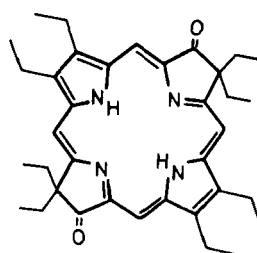
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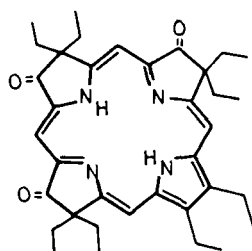
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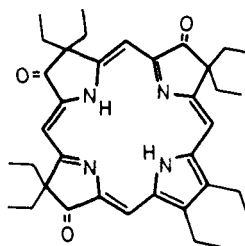
58



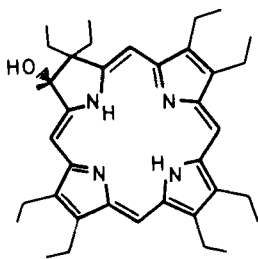
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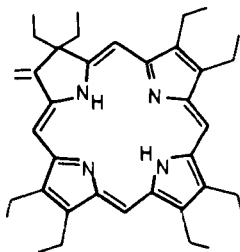
60



61



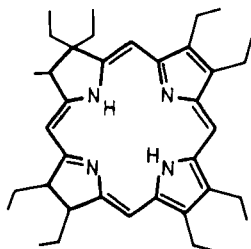
62



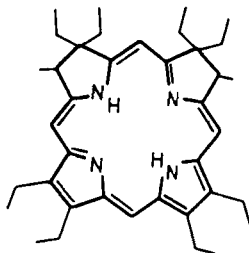
63

Reaction of oxochlorin **54** with methyllithium gave alcohol **62**, which was dehydrogenated to the exomethylenechlorin **63** (69LA(725)167). Oxohydroporphyrins have found multiple interest. A knowledge of the properties of **56** may help to elucidate the structure of heme d_1 , which most probably is a dioxoisobacteriochlorin and not a chlorin (86JA1352).

Methyloctaethylchlorin (**64**) was obtained from the oxochlorin **54** with methyllithium to give an alcohol, which was reduced with hydroiodic acid. Similarly, the isobacteriochlorins **9** and **65**, which are models of siroheme and sirohydrochlorin, were obtained from dioxo derivatives **55** and **57** (80B1971).

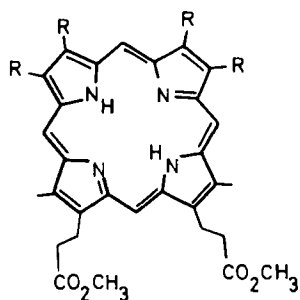


64

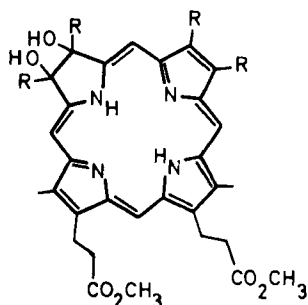


65

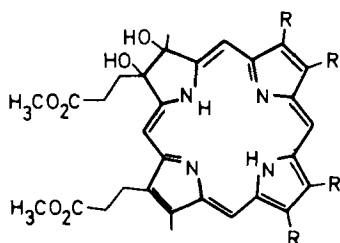
Information on the regioselectivity of the OsO_4 route came from a synthesis of a heme and Bonellin model compound. Oxidation of the porphyrin **66a** resulted in a mixture of 37% **67a** and 8% **68a**. The OsO_4 attack is prone to steric influences. The more bulky peripheral ethyl groups in **66b** cause the formation of nearly equal amounts of **67b** and **68b**. Rearrangement of the glycols **67** into the oxochlorins **69** and **70** was cleanly performed with 70% HClO_4 ; the yields of the isomers formed were similar. From **70a**, the target molecule **71b** was obtained by Wittig olefination (to give **71a**) and hydrogenation (85JOC4989).



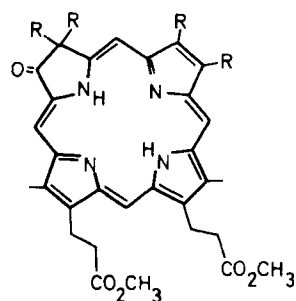
66a $R = \text{CH}_3$
 66b $R = \text{C}_2\text{H}_5$



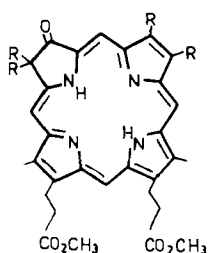
67a/b



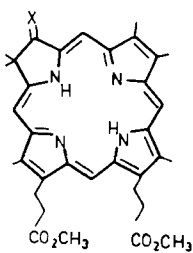
68a/b



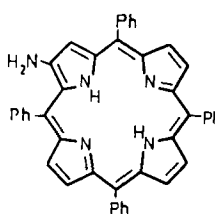
69a/b



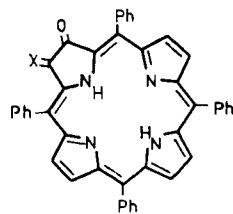
70a/b



71a $x = \text{CH}_2$
 $x = \text{H}, \text{CH}_3$

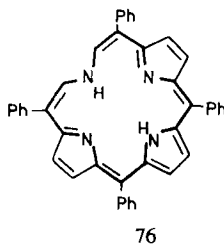
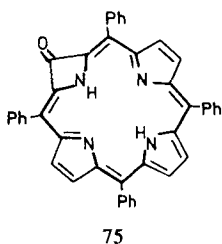
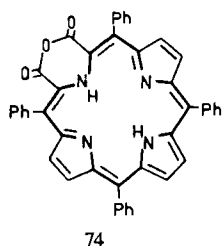


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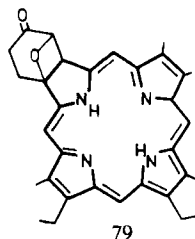
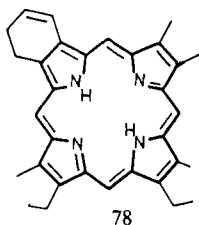
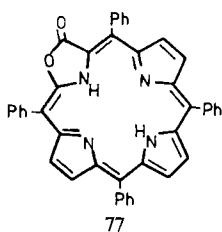


73a $x = \text{NH}$
 73b $x = \text{O}$

Photooxidation of suitably substituted porphyrins sometimes results in formation of hydroporphyrins. Thus, photooxidation of 2-amino-TPP (**72**) gave **73a**, which was hydrolyzed to **73b**. Oxidation of the ketone **73b** gave a mixture of **74** (80%) and **75** (4%; ν_{CO} 1780 cm^{-1} ; m/e 616; c_{2v} symmetry from



NMR spectra). Attempts to degrade **74** to the chlorophin **76** were not successful. Oxidation of **72** with *m*-chloroperoxybenzoic acid (MCPBA) gave the lactam **77** (84CC920).

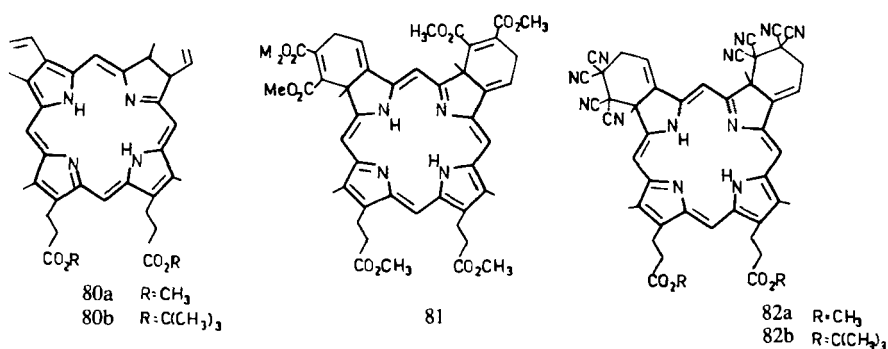


In Scheme 1 (Section IV,A,2), a photooxidative transformation of a peripheral methyl group into a formyl group was described. This occurs in a hydroporphyrin derivative with interrupted conjugation. The mechanism of this synthetically important reaction has been investigated (82JA516). Secondary reactions of a photochemical primary product may vary, as can be deduced from a photooxidation of the cyclohexadienoporphyrin **78**, yielding a product of a tentatively assigned structure **79** (82AJC197).

D. CONTRACTION OF THE PORPHYRIN π -SYSTEM BY NONREDOX ROUTES

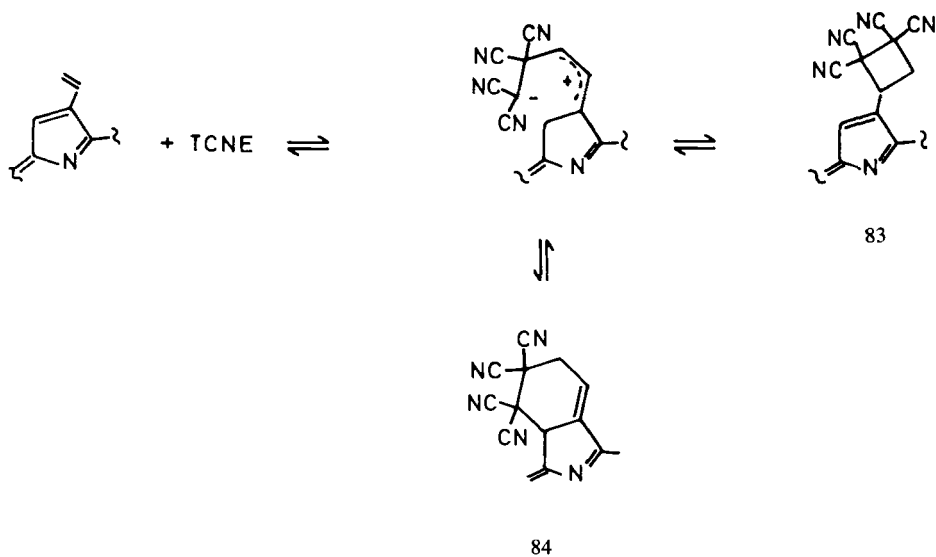
Olefinic reactions may occur at cryptoolefinic peripheral double bonds of porphyrins and, sometimes more easily, of metalloporphyrins.

It was demonstrated some time ago that vinylic and cross-conjugated double bonds of protoporphyrin (**IX**) dimethyl ester (**80a**) constitute a diene system capable of undergoing Diels–Alder reactions with activated dienophiles (68CC697). Isobacteriochlorins **81** and **82a** were obtained in a reaction with dimethyl acetylenedicarboxylate (ACDE) and tetracyanoethene (TCNE), respectively (73JCS(PI)1424).

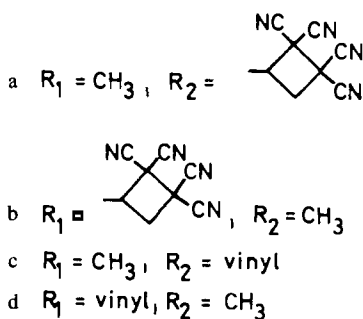
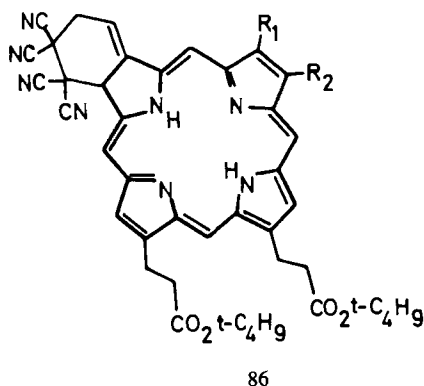
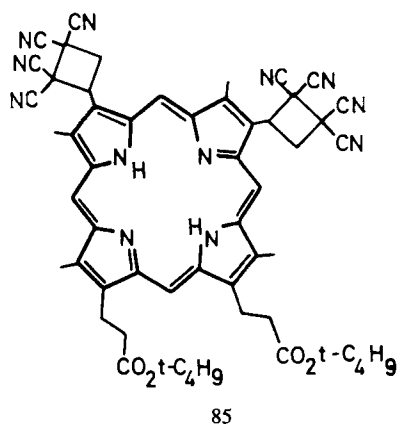


A detailed investigation of the reaction of protoporphyrin **80b** with TCNE in chloroform demonstrated the kinetically controlled formation of [2 + 2]-adducts (**83**), which either rearranged to [4 + 2]-adducts (**84**) or lost TCNE in a cycloreversion. A dipolar intermediate was assumed for these reactions (Scheme 4). Depending on reaction conditions, [2 + 2]- (**85**), [4 + 2]- (**82**, **86c,d**), and mixed-type (**86a,c**) adducts were obtained (80JOC5196). Regio- and stereospecificity of the Diels–Alder reaction of **80b** with unsymmetric acetylenes has been studied (86JOC1094).

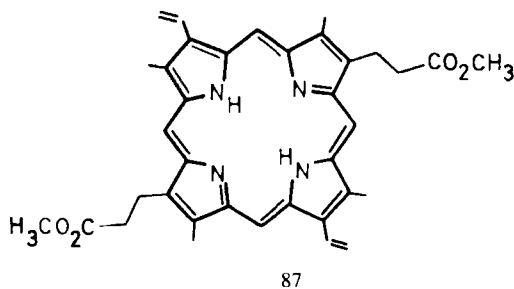
Elimination of the angular methyl group from [4 + 2]-adducts of **82** gave monobenzoporphyrins (84CC1047).

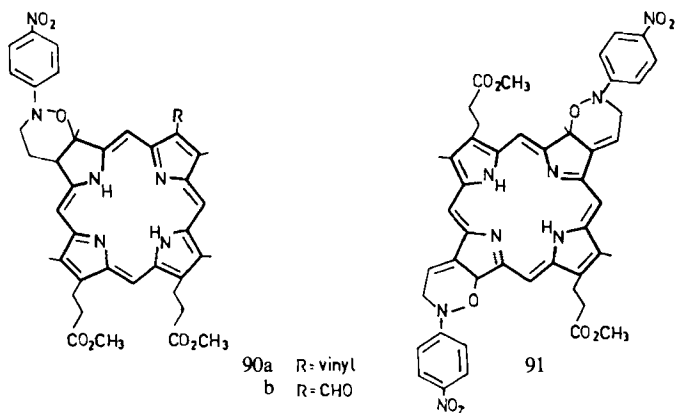
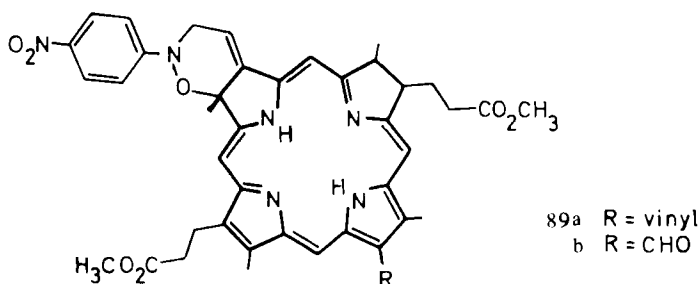
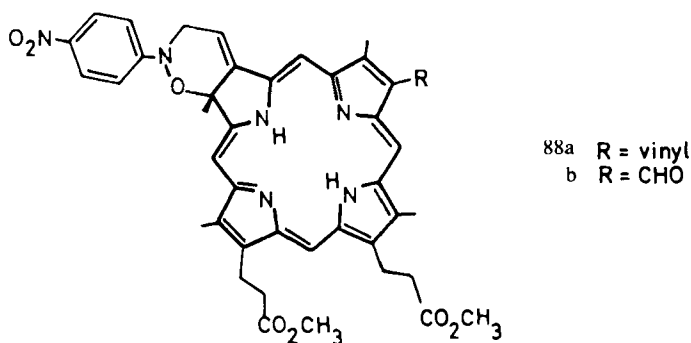


SCHEME 4

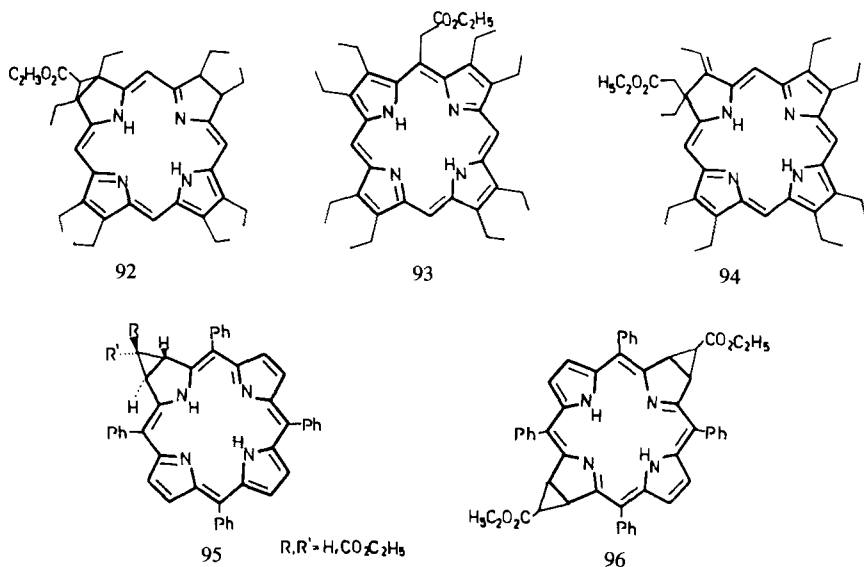


From divinylporphyrins **80** and **87**, [4 + 2]-cycloadducts **88a** and **89a** were obtained with *p*-nitronitrosobenzene, together with aldehydes **90** and **89b**. No diadduct of isobacteriochlorin was obtained from **82**, which was attributed to the low π -stabilization of isobacteriochlorin. The more stable bacteriochlorin **91**, however, could be obtained from **87** (85CC776).



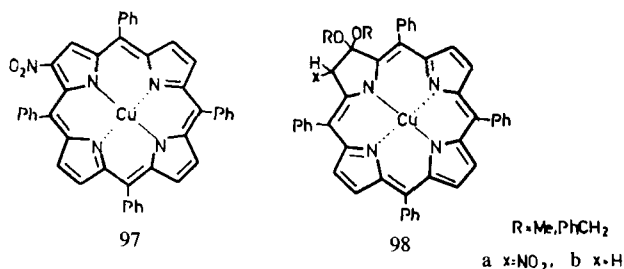


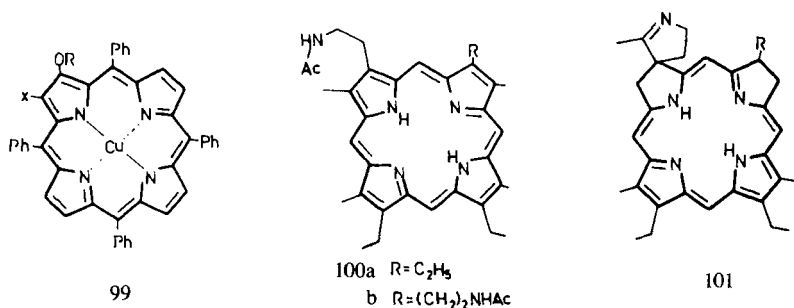
Addition of carbenes to peripheral porphyrin double bonds has been studied. OEP (**11**) fails to react with ethyl diazoacetate, even in the presence of copper(I) iodide. The Cu–OEP, however, gave two isomeric Cu–isobacteriochlorins, which were demetallated to **92**. Small amounts of a meso product **93** were also observed. A photochemical isomerization of **92** resulted



in formation of the exomethyleneisobacteriochlorin **94** (73JCS(PI)1424). In a similar reaction, Zn-TPP yielded after demetallation the cyclopropano-chlorins **95** and bacteriochlorin derivatives **96** (72BSF4387). Interestingly, no isobacteriochlorin derivatives were obtained from metal complexes of porphyrins and carbenes.

Sometimes special structural features render possible a reduction of the porphyrin π -system. Chlorins **98a** were obtained from the Cu complex **97** by nucleophilic addition to a peripheral double bond activated by a nitro group. Reductive denitration occurred on treatment of **98a** with tributylstannane. The chlorins **98b** can be easily transformed into alkoxy porphyrins **99**, which are enol ethers of oxohydroporphyrins and are treated in Section IV,C (84CC1537).





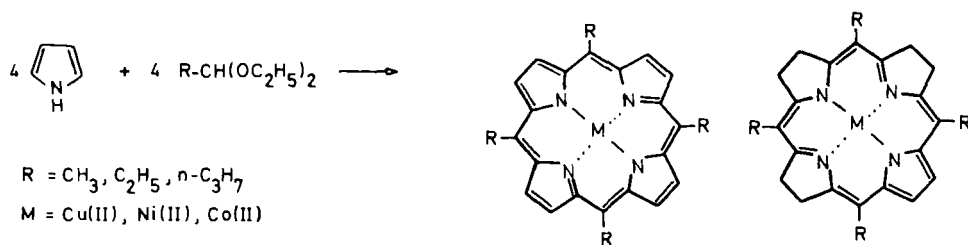
Chlorins **101** were generated by intramolecular electrophilic attack at a peripheral position of porphyrins **100** with phosphoryl chloride in pyridine (66CC299).

E. RING SYNTHESSES

During the last decade a remarkable number of hydroporphyrins have been synthesized, mostly with regard to biochemical problems. Ring synthesis proves particularly important in this area since a possible control of single steps of the synthetic sequence allows for an establishment of a specific substitution pattern. Examples of this section are presented in a file of decreasing size of the π -systems, i.e., chlorins are followed by bacteriochlorins, etc.

1. Chlorins

In syntheses of *meso*-tetraalkylchlorins, problems arise with contamination by chlorins. A template synthesis was described wherein the ratio of porphyrin and chlorin complexes formed can be controlled by the metal and the amount of the anhydride used (Scheme 5). Demetallation of complexes was

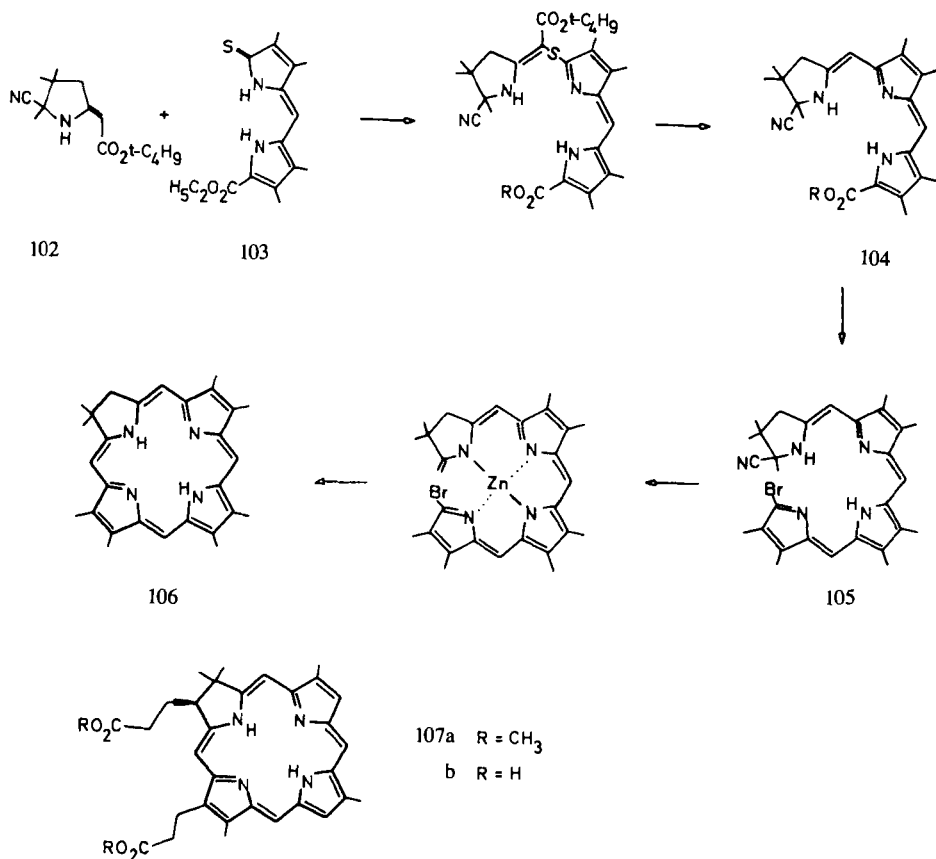


SCHEME 5

achieved by standard techniques [examples include $M = \text{Ni}$, 5% Ac_2O gave Ni-TMC (1.9%) only; $M = \text{Cu}$ gave Cu-TMC (2.0%) only; and $M = \text{Co}$ gave Co-TMP only (80JA6852)].

Apart from Woodward's chlorophyll syntheses (60AG651) and Inhoffen's route to chlorophyll trimethyl ester (**31**) (Section IV,A,2), selective syntheses of interesting natural chlorin derivatives have been rare. This situation has changed remarkably recently.

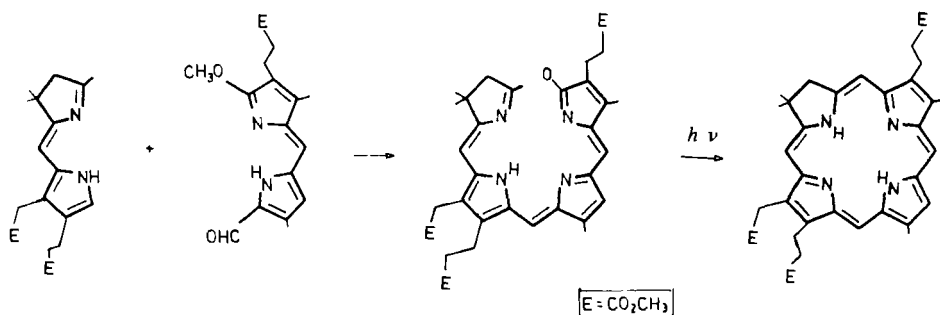
In Scheme 6, a controlled synthesis of OMC (**106**) by Montforts is portrayed (85LA1228). Treatment of **102** with *N*-bromosuccinimide (NBS) led to bromination of the enamine double bond, thus enabling coupling with **103** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Sulfur contraction led to the tricycle **104**, which, following transformation into an Ni complex and



SCHEME 6

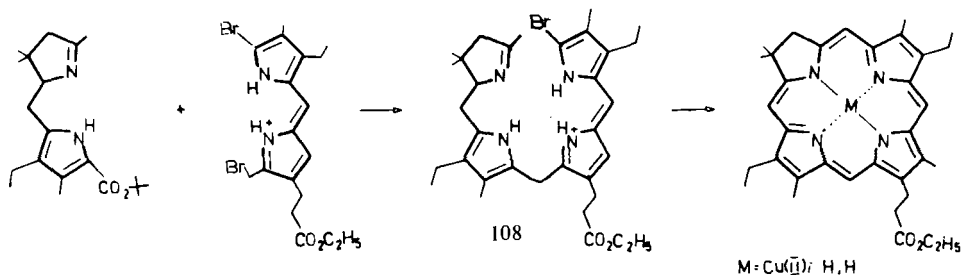
saponification of the ester group, could be coupled with the corresponding bromoaldehyde to give the tetracyclic linear compound **105**. Final cyclization occurred on treatment with sodium *tert*-butylate/Zn-acetate followed by acidic work-up. A successful total synthesis of (\pm)-bonelline dimethyl ester **107a** is based on this strategy (85AG(E)775).

A photochemical cyclization gave high yield of chlorins, as depicted in Scheme 7 (83CC1235). The reaction is also used for an efficient synthesis of **107a** (83CC1237).

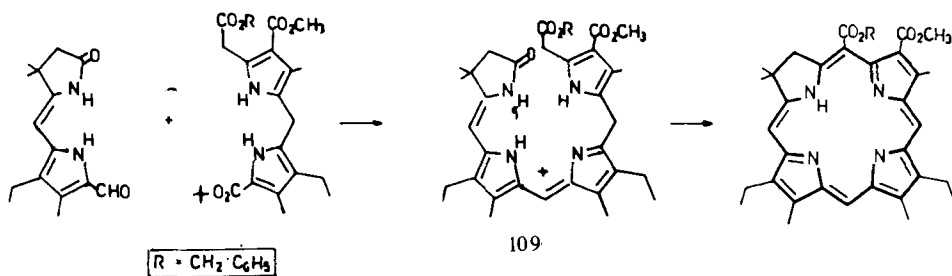


SCHEME 7

Extensive studies relevant to biosynthetic research on vitamin B₁₂ originate from Battersby's group (84JCS(P1)2725, 84JCS(P1)2733). In Schemes 8 and 9, two routes are presented. The first synthesis (Scheme 8), though not high yielding, involves only a few steps from readily accessible building blocks. Ring closure of **108** occurred with Cu(II) acetate in acetonitrile; copper was removed by trifluoroacetic acid (TFA) saturated with hydrogen sulfide. Cyclization of **109** was achieved by conversion with Meerwein salt into the imino ether, which with Cu(II) acetate in hot acetonitrile gave the Cu(II)-chlorin. Demetallation was carried out as described before.



SCHEME 8



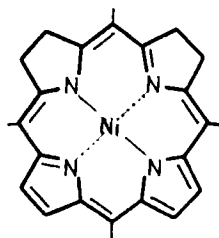
SCHEME 9

2. Bacteriochlorins

It has been claimed that heating of an *o*-dichlorobenzene solution of 2-(dimethylaminomethyl)pyrrole with an oxygenated Grignard reagent for 10 hr at 160°C gives a mixture of porphyrin and isobacteriochlorin (67JGU333). Reaction products were characterized only on the basis of their electronic spectra and no yields were reported.

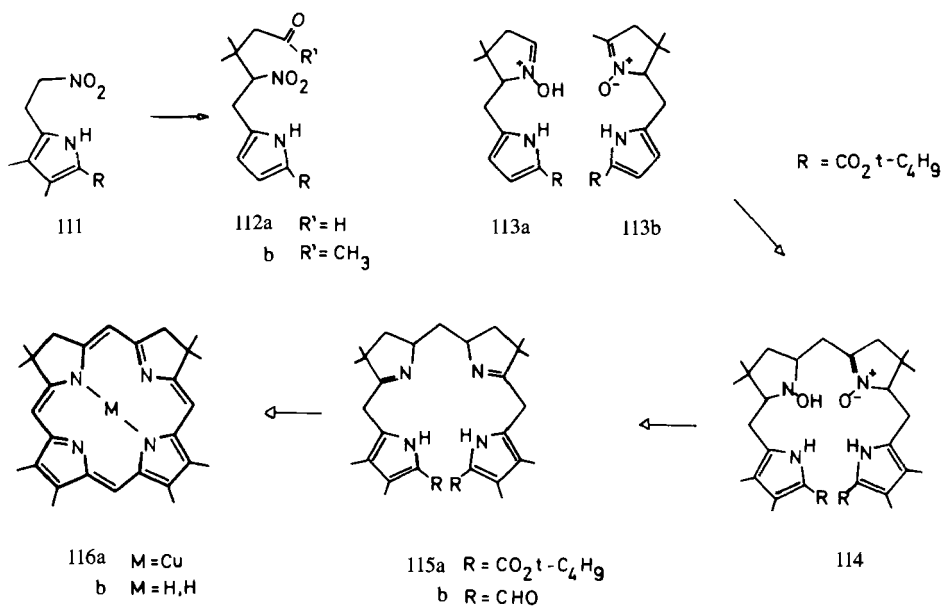
3. Isobacteriochlorins

Ni-TMiBC (**110**) was obtained from pyrrole and acetaldehyde diethylacetal in an acetic acid solution of Ni(II) acetate under an inert atmosphere in a yield of about 1% based on Ni (84JA5164).



110

An approach to OMiBC (**116b**) (Scheme 10) was described (84JCS-(PI)2743). The synthesis of both the "western" and the "eastern" part of **113** starts from the nitropyrrole **111** via the oxo derivatives **112**. Coupling of **113a** and **113b** to **114** occurred on treatment with sodium hydride in THF. Reduction of **114** followed by dehydration gave **115a**, which then was transformed to the aldehyde **115b** and cyclized with Cu(II) acetate to give **116a** (16% from **115a**) and, after demetallation, **116b**.



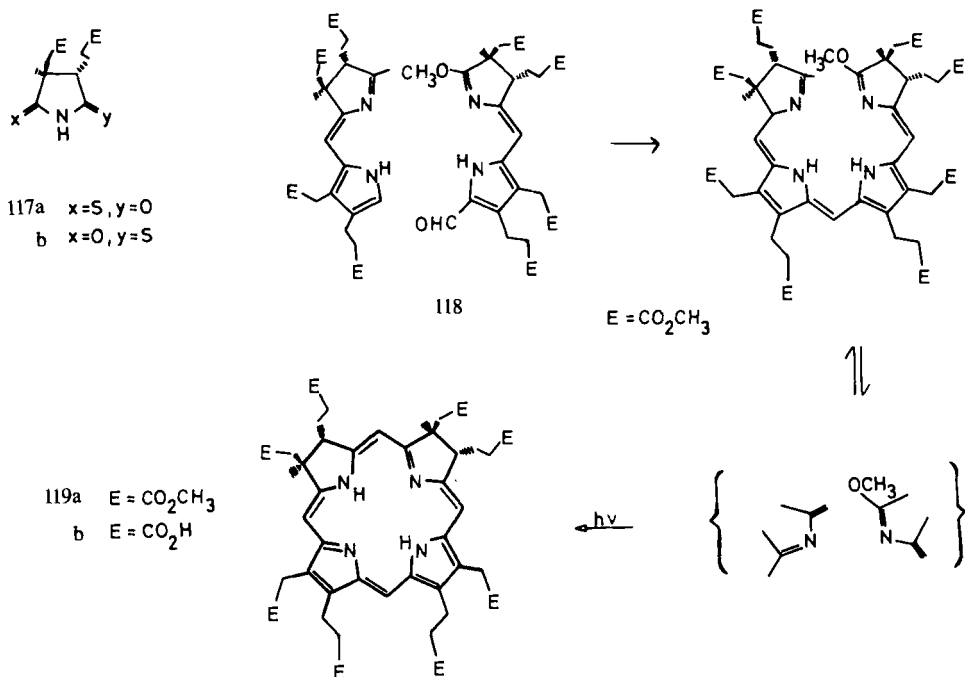
SCHEME 10

A photochemical route to OMiBC (**116b**) has been developed which is similar to that described in Section IV,E,1 (Scheme 6) (81CC797). The method was applied to a synthesis of the natural enantiomer of sirohydrochlorin **119**, as shown in Scheme 11 (85CC1061). Interestingly, the two sides of **118** were prepared from thioimides **117**, resulting from one imide by Wittig olefination. Isobacteriochlorins substituted in position-20 were prepared using a similar strategy (84CC525) as was (\pm)-factor-I octamethyl ester (85CC583).

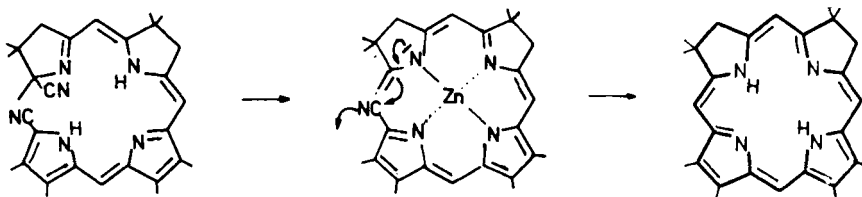
The crucial step of the synthesis of OMiBC's developed in the Eschenmoser group is a reaction of a pyrrole bearing a leaving group in an α -position with an enamine on the other side of the molecule (80AG(E)143). The route to chlorins being isomeric to **116** is shown in Scheme 12 (81HCA1431). Cyclization was performed at 145°C in sulfolan in the presence of Zn(II) acetate and DBU. Decomplexation took place with TFA yielding 73% of the isobacteriochlorin.

4. Pyrrocorphins

Synthesis of the pyrrocorphin **122** (Scheme 13) was rendered difficult by the instability of the intermediates, as well as of the product. Sulfur contraction of **120** and imino ether condensation of **121** could be effected only by using appropriate complexes (82HCA600).



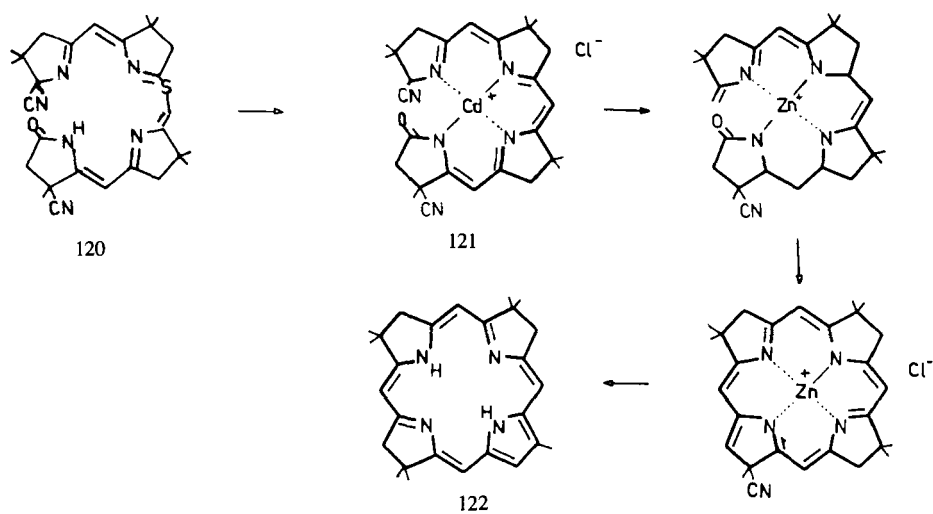
SCHEME 11



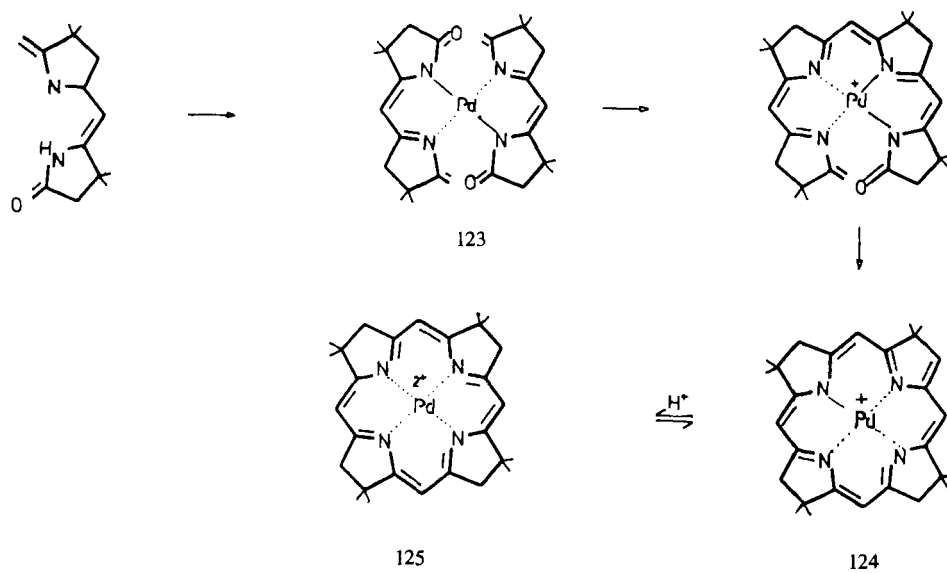
SCHEME 12

5. Corphins and Systems with Interrupted Conjugation

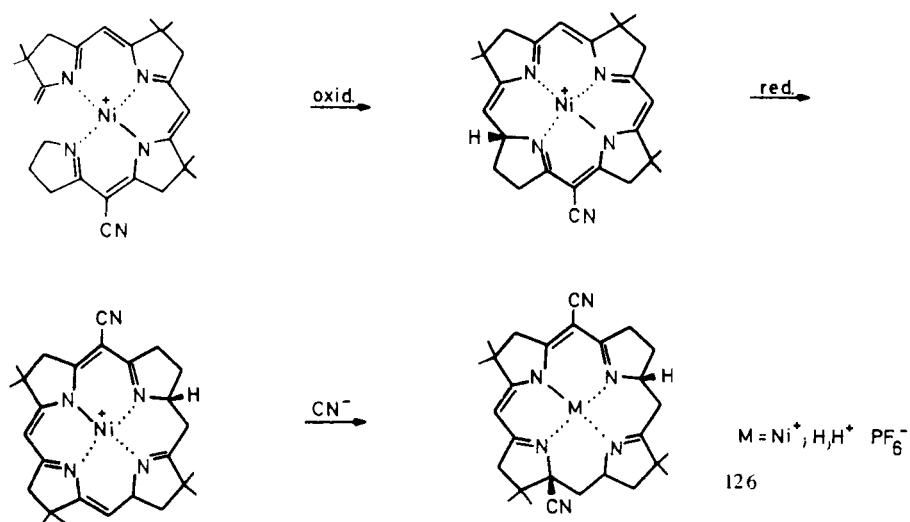
The nearly planar structure of Pd(II) complex **123** enabled a twofold connection of the bicyclic units in imino ether condensations brought about by Meerwein's salt and diisopropylethylamine in methylene chloride. Protonation of **124** (Scheme 14) generates a Pd(II) complex (**125**) of an octahydroporphyrin, with complete saturation of the peripheral double bonds containing the π -system of 1,5,9,13-tetraaza[16]annulene (68AG622).



SCHEME 13



SCHEME 14



SCHEME 15

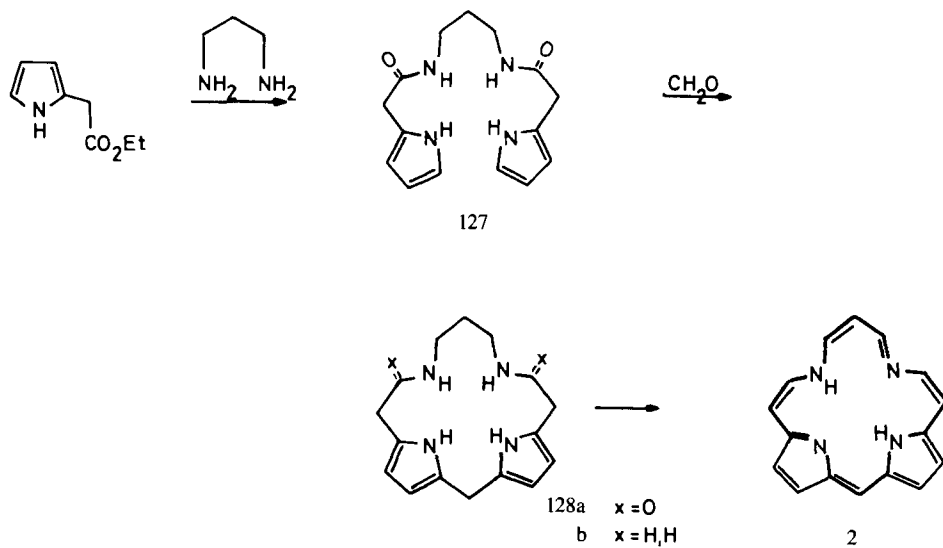
A tetrahydrocorphin (**126**) containing the chromophore system of coenzyme F-430 was synthesized using electrochemical redox reactions (Scheme 15) (84CC1365). Attention is drawn to the original paper for mechanistic details.

6. Norporphins

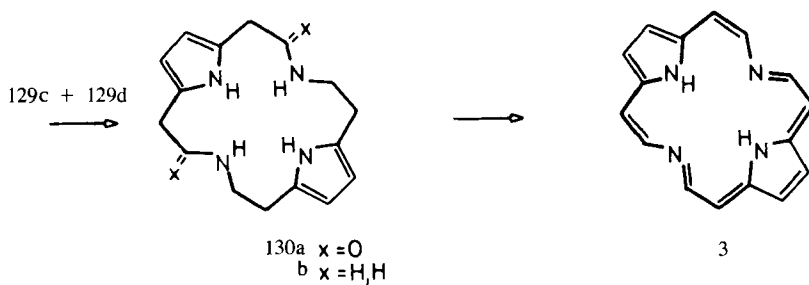
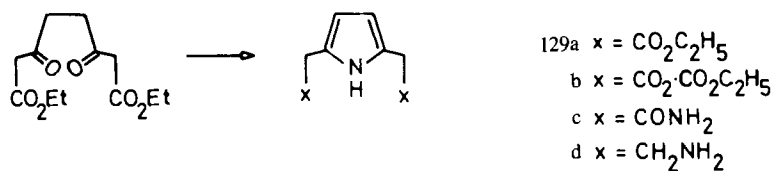
Norporphins **1–4** are parent compounds of hydroporphyrins. Isobacteriophin (**2**) (Scheme 16) and bacteriophin (**3**) (Scheme 17) have been synthesized (86PAC153). Attempts to synthesize chlorophin derivative **76** failed (see Section IV,C).

The crucial step of the synthesis of isobacteriophin **2** (i.e., cyclization of **127** with formaldehyde) surprisingly did not require a high-dilution technique. Reduction and thermo-flash dehydrogenation of **128a** gave 2% **2**; dehydrogenation of a Cu(II) complex of **128b** in solution led to 12% Cu(II)—**2** (85LA1004).

The synthesis of the macrocycle **130a** with the topology of a bacteriophin on the other hand required a high-dilution technique. A subsequent reduction to **130b** followed by thermo-flash dehydrogenation gave bacteriophin **3**, albeit in poor yield (0.2%).



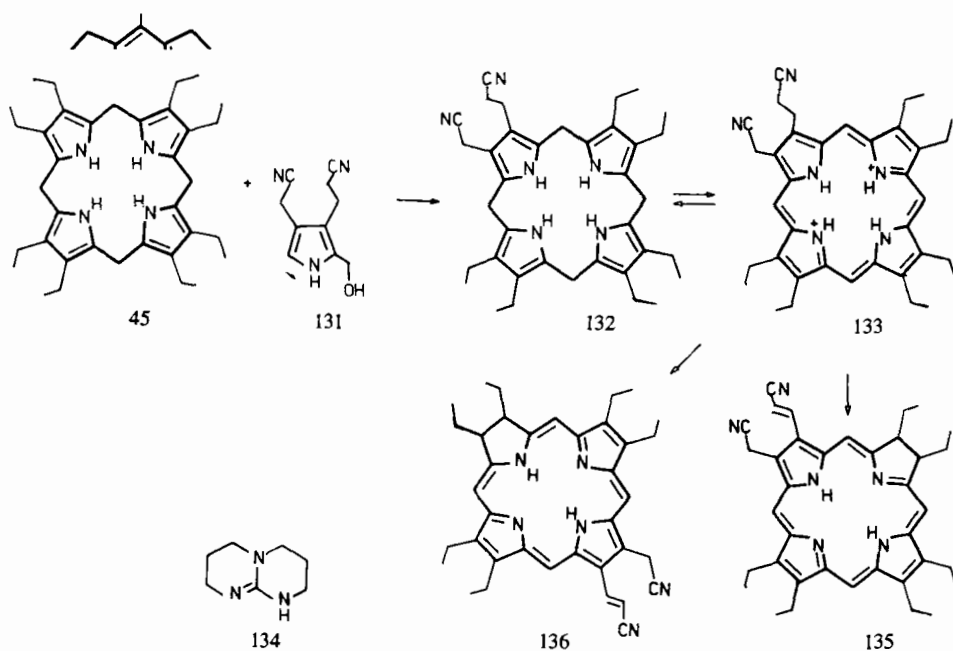
SCHEME 16



SCHEME 17

F. MISCELLANEOUS METHODS

One pyrrole ring of OE-porphyrinogen (**45**) was replaced in an acid-catalyzed reaction with the hydroxymethylpyrrole (**131**) (Scheme 18). The resulting porphyrinogen (**132**) was dehydrogenated to the porphyrin (**133**), which, on heating in the molten guanidine base **134**, was subjected to a disproportionation reaction yielding 43% of the porphyrin **135** together with 5% of the porphyrinogen **132** and 4% of the chlorin **136** (85TL5899).

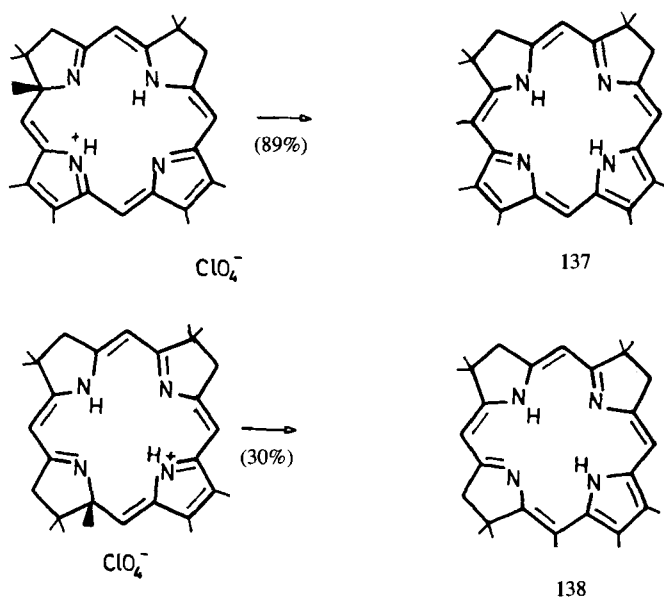


SCHEME 18

A sigmatropic methyl shift from an angular to a meso position (Scheme 19) is the crucial step in synthesis of the isobacteriochlorin **137** and the pyrrocorphin **138** (83CC1401).

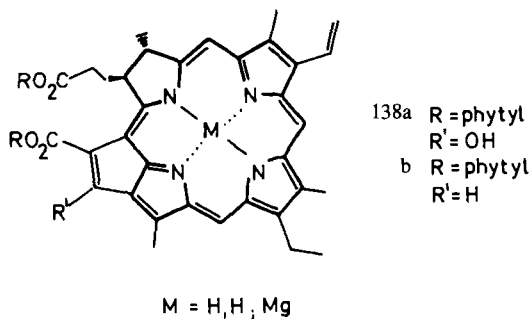
V. Biochemical Aspects

Only a rough draft of the biochemistry of hydroporphyrins will be given here, pointing out some problems which have stimulated chemical investigations.



SCHEME 19

The roles of chlorophylls and bacteriochlorophylls (i.e., chlorin and bacteriochlorin derivatives) in photosynthesis is well established. The enolic tautomer of the β -keto ester in ring V of chlorophyll *a* (**138a**) has been suggested as a possible intermediate in the photochemistry of *P*-700 chlorophyll, found in green plant photoreaction centers. A new stable analogue (**138b**) was described which possesses a π -system very similar to that of the enol, thus serving as a useful model for photochemical studies. The meso protons of **138b** are shifted to high field by nearly 2 ppm relative to those in **138a**. Differences resulting from an enlargement of the chlorin chromophore appear also in electronic spectra (78TL1043).



Cytochromes and other proteins believed to contain iron chlorins were reviewed (85JA4207; 85JA6069).

The iron complex of sirohydrochlorin (**119b**) is the prosthetic group of nitrite (81MI1) and sulfite reductases (75M17). These enzymes catalyze six-electron reductions yielding ammonia (sometimes NO, N₂O, and N₂) and hydrogen sulfide, respectively.

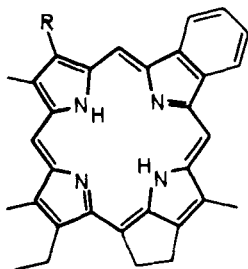
Heme *d*₁ isolated from *Pseudomonas aeruginosa* and *Paracoccus denitrificans* was proposed not to be a chlorin but a 3,8-dioxoisobacteriochlorin similar to compound **55**. This was confirmed by a comparison of the chromophore with that of a model compound (86JA1352).

A particularly striking example of the importance of hydroporphyrins in nature is represented by the biosynthesis of vitamin B₁₂ (85MI1). Some aspects of this metabolism outlined in Scheme 20 indicate that nearly the whole family of hydroporphyrins takes part in the reaction sequence either as intermediates or as equilibrating isomers. Biochemical problems in this field gave rise to many of the chemical activities described here.

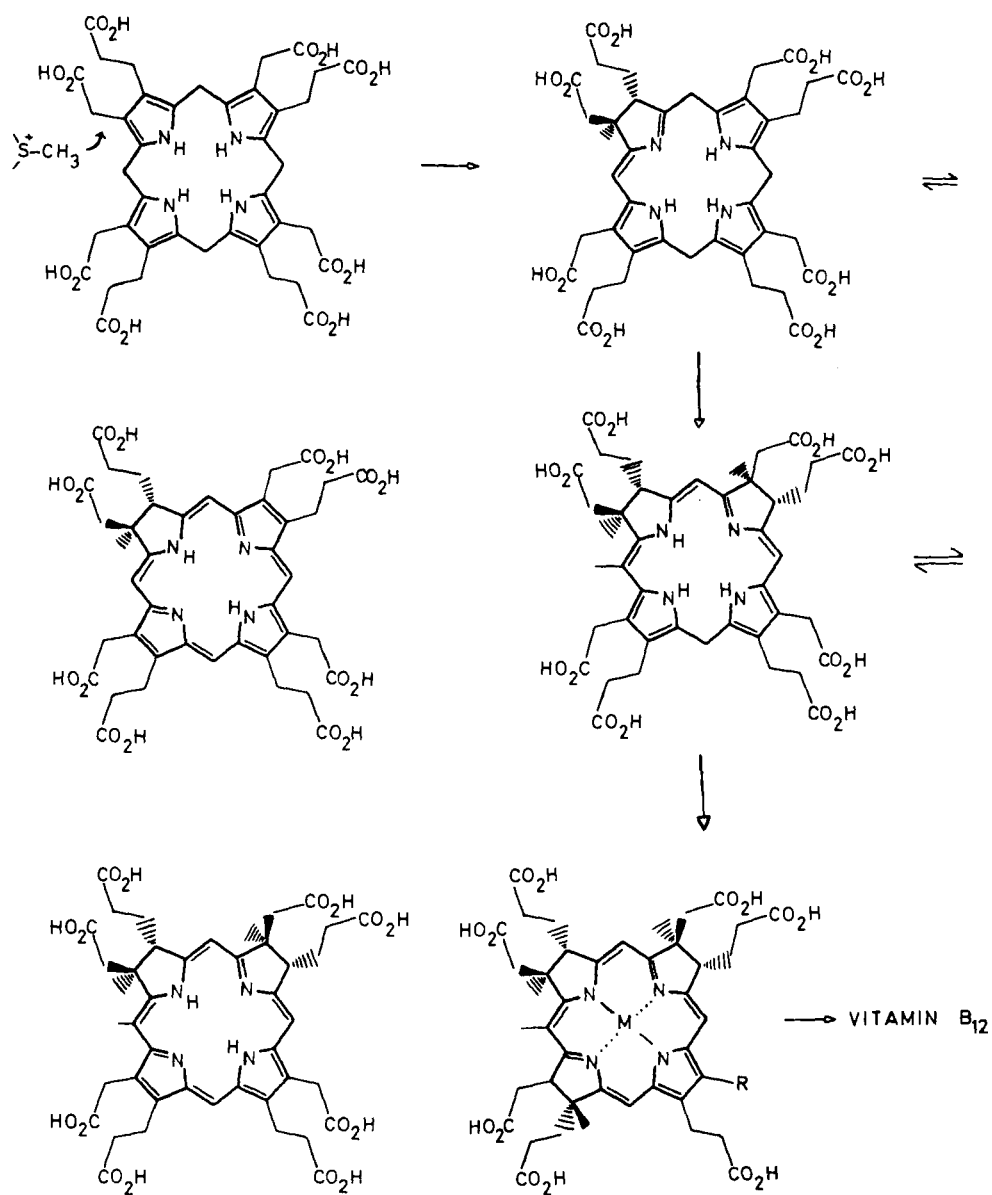
The reaction sequence shown in Scheme 2 mimicks a step of chlorophyll biosynthesis as well as hydrogen formation as a part of photosynthesis (82AG(E)132).

Structure **22** of the hydroporphyrin ligand system of factor *F*-430 has been elucidated mainly by a combination of incorporation and ¹³C-NMR experiments (82HCA828; 84HCA334). Isomerization of **22**, which may occur during work-up was mentioned in Section III, D (85HCA1338). Factor *F*-430 (**22**) contains a chromophore system not previously encountered among natural products.

Monobenzoporphyrins (**139**) were isolated from crude oil and their structure was assigned by ¹H-NMR spectroscopy. It is clear from the substitution pattern that sedimentary porphyrins have arisen from chlorophylls rather than from tetrapyrroles, but the position of the benzene ring excludes an origin from any known chlorophyll either by a Diels–Alder



139 R = CH₃, C₂H₅



SCHEME 20

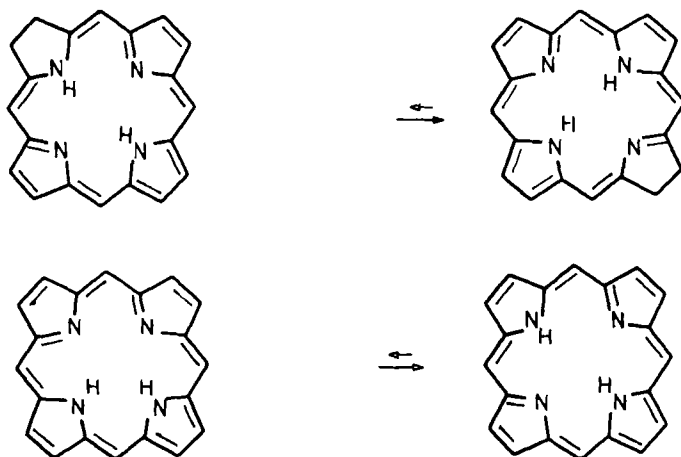
reaction of a type discussed in Section IV,D or by a cyclization involving adjacent methyl and propionic acid chains. It has been suggested, therefore, that the benzoporphyrins have originated from a precursor related to bacteriochlorophylls *d* (86JA1348).

VI. Conclusion and Outlook

The question of the most relevant (delocalized) conjugation pathway in porphyrins (75M18) sometimes still causes confusion. Thus, meso reactivity of porphyrins toward electrophiles is frontier orbital controlled. This (75M15) has been taken as evidence for Fleischer's model of an internally delocalized π -system, as shown in structure **XVIII** (84T2359).

The properties of hydroporphyrins described here and numerous investigations of porphyrins render possible some generalizations concerning the structure of these chromophores.

1. Internal hydrogens are located at opposite nitrogens. Hydrogens at adjacent nitrogen atoms give rise to steric strain, causing strong deviations from planarity. Two examples are given in Scheme 21.



SCHEME 21

2. Delocalization of the chromophore is as indicated in **XVII**. Porphyrins and porphinooids closely resemble the 18-membered 18 π -electron [18]annulenes, avoiding energetically unfavorable conjugation via pyrrolic nitrogen lone pairs. If interactions of this type are necessary for structural reasons [as in

pyrrocorphin (V)], the π -system does not contribute substantially to a stabilization of the molecule.

3. As a consequence of the tendency of porphinoids to form an 18 membered 18 π -electron delocalization circle, NH-groups will be found preferentially at pyrrolic rings trying to avoid the nitrogens of hydrogenated pyrroline rings.

4. Peripheral double bonds of porphyrins are cryptoolefinic, as reflected in structure (Section II, B), spectra (Section II, C), and chemical properties (Section III). From UV and NMR spectra at low temperatures, indications of differences between localized and delocalized peripheral double bonds have been deduced. A rapid isomerization at room temperature may be anticipated.

These rules are corroborated by HMO calculations (86VP1); experimental proof, however, is still missing in some cases.

The chemistry of hydroporphyrins has been investigated so far mainly in view of biochemical problems. Only small amounts of hydroporphyrins, especially those with selected substitutions patterns as, e.g., parent compounds, are accessible by the routes described. Progress in biochemistry as well as in essential chemical and physicochemical investigations thus strongly depends on developments in the synthetic field.

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Reactions of Annular Nitrogens of Azines with Electrophiles

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I. Introduction

The monocyclic diazines, triazines, and tetrazines are all theoretically subject to electrophilic attack at one or more of their annular nitrogen atoms by protons; alkylating, acylating, and aminating reagents; and peracids. Coordination with metals could also be classified under this heading.

Many of the reactions have been surveyed recently in *Comprehensive Organic Chemistry* (79MI1) and *Comprehensive Heterocyclic Chemistry* (84MI1), and there have been a number of other review articles dealing with aspects of these reaction types (59HC1; 60RCR437; 62HC1; 64AHC1; 65AHC69; 67AHC115; 68AHC211; 70HC1; 70MI1; 71MI1; 72AHC99; 73HC1; 76AHC1; 76AHC215; 78AHC71; 78HC3; 78HC189; 78HC1287; 79AHC363;

82HC1; 83AG(E)171; 85AHC229). This article amplifies and updates current knowledge of this material, with the exception of metal coordination.

Wherever possible we attempt to emphasize any quantitative studies which come within the scope of the review, and to collate data on regiochemical effects of substituents in the azine rings. It is unfortunate that some of the quantitative information about yields of isomeric products was reported before the use of modern physical methods became routine. Accordingly, some of the data must remain suspect, as do some of the structures reported.

II. Protonation

All of the azines are weak bases, in which the natures and positions of substituents alter the ease and orientation of N-protonation. This review does not aim to provide a comprehensive survey of basic characteristics within the series, but merely highlights the reactivities of particular ring nitrogen atoms with proton acids, since these reactivities are frequently related to trends observed in N-alkylation, N-acylation, and N-oxidation.

In spite of their weakly basic nature, the azines often form salts with mineral and other strong acids, although these salts may not be stable, particularly when covalent hydration can accompany or compete with protonation. Thus, whereas pyridazines (68AHC211) and pyrazines (69JCS3156) readily form salts with strong acids [the latter can even form di-salts with proton acids and dicoordination compounds with Lewis acids (69JCS3156)], triazines and tetrazines are much less stable in acidic medium. The rings are commonly destroyed when 1,3,5- (75ZOR2613), 1,2,3- (60TL19), and 1,2,4-triazines (70JHC767) are left in the presence of strong acids. Tetrazines are even less stable at low pH. Whereas triaryl-1,2,3-triazines are protonated at N-2 when they form salts with aqueous hydrochloric acid at room temperature, higher temperatures cause ring fission with generation of 1,3-dicarbonyl products (60TL19). The use of dry acid in an organic solvent has been recommended for forming 1,2,4-triazine salts, and 5,6-diphenyl-1,2,4-triazine gave a crystalline hydrochloride when treated with concentrated hydrochloric acid in concentrated sulfuric acid solution (54CB1540). On the other hand, trifluoroacetic acid appears to hydrate 1,2,4-triazine covalently (70JHC767); 1,3,5-triazine is similarly susceptible to this type of attack (75ZOR2613).

When pK_a comparisons are made among the diazines (pyridazine, 2.33; pyrimidine, 1.31; pyrazine, 0.60, but variously reported in the range 0.5-1.1), it is obvious that the 1,2-diazine is the most reactive with acids. Substituents can vary these values considerably (64AHC1; 65MI1; 77MI1; 84MI2; 84MI4) and

also affect the regiochemistry of protonation. The triazines and tetrazines are much less basic and show pronounced basic qualities only when there are electron-donating substituents present (e.g., 1,2,4-triazine-3,5-dione, pK_a 6.99; 2-methyl-1,2,4-triazine-3,5-dithione, pK_a 5.76). In the 1,2,4-triazines, protonation can occur at N-1 or N-4 (78HC189; 84MI4); 1,2,3-triazines react with protons at N-2 in the first instance (79CB1514).

Correlations of pK_a - σ relationships in the series using the equation

$$pK_a = \sigma_I \rho_I + \sigma_R \rho_R + c$$

where subscripts I and R refer to inductive and resonance, respectively, suggest that it is necessary to build separate series for +M and -M substituents, and to allow for their regiochemistry, since substituents of the same resonance type can exert quite different influences from different ring positions (77MI1). In general, pK_a values of azines are most sensitive to α -substituents, followed in turn by β and γ , demonstrating that inductive effects are most important (about 70% of the total electrical effects of α -substituents are inductive). Resonance effects become more important with para substituents. The ρ_I/ρ_R ratios for +M substituents are: 3-(+M)-pyridazines, 2.61; 4-(+M)-pyridazines, 1.23; 2-(+M)-pyrimidines, 2.08; 4-(+M)-pyrimidines, 1.32; 2-(+M)-pyrazines, 1.68 (77MI1). In addition, substituent effects are not completely additive. A selection of pK_a data for substituted pyridazines illustrates some of these features (Table I). Different substituents often direct protonation to different annular nitrogens. Thus, 3-chloropyridazines are protonated at the more remote N-1, 3-aminopyridazines at N-2 (76JCS(P1)1424), and

TABLE I
 pK_a VALUES OF PYRIDAZINES^a

Substituent	pK_a	Substituent	pK_a
H	2.33	3-SMe	2.26
4-Me	2.92	4-SMe	3.26
3,6-Me ₂	1.61	3-NH ₂	5.19
3-OMe	2.52	4-NH ₂	6.69
4-OMe	3.70	3-NH ₂ -6-Me	5.32
4-OH ^b	1.07	3-OH-6-Me ^b	-0.81
3-OH ^b	-1.40	3-OH-6-Cl ^b	-2.01
3-Cl-6-Me	0.89	3-NMe ₂	4.59
3,6-Cl ₂	-1.50	3,6-(NMe ₂) ₂	6.71
3-Cl-6-Ph	-0.06	3-Cl-6-NMe ₂	2.82

^a 59JCS1253, 64AHC1, 72JCS(P2)392, 77MI1, 84MI2.

^b Hydroxy compounds may exist largely as the oxo tautomers.

3-pyridazinones protonate on the oxygen to some degree (79AJC2297). Studies of protonation of pyridazinones give a smaller spread of results using H_A rather than H_O (72JCS(P2)392; 79AJC2297).

It is possible to use ^{13}C - and ^1H -NMR coupling constants to detect protonation sites in nitrogen heterocycles (77JA6838; 81JCS(P2)783), while ^{13}C -chemical shifts, which are very sensitive to protonation effects, have been used to estimate proportions of 1- and 3-pyrimidinium species (77JA6838). Another method (81CC1224), based on the decrease in the vicinal (^{13}C , ^1H) coupling constant values across the protonated nitrogen, and corrected to allow for differences between the model methylated forms and the protonated forms, showed that 2-amino-4-methylpyrimidine is 66% protonated at N-1, whereas the 2,4-diamino derivative is 100% protonated at N-1 (83CC105); this is a greater N-1 population than previously determined (81CC1224), and one in better agreement with ^{13}C -NMR shifts (77JA6838). With 4-dimethylaminopyrimidine, the +M effect directs predominant protonation to N-1 (80CJC466).

Good correlations between $\text{p}K_a$ and σ_m values were obtained for 5-substituted pyrimidines, again pointing out a major inductive influence from that position (66CPB1321; 66JOC1199). Reaction constants were not very different from those found in studies of pyridine basicity (55JA4441). Again, however, there was a significantly greater resonance component than allowed for by σ_m constants, and the best correlations were obtained (69JOC821) by use of the equation

$$\log(K/K_0) = \rho(0.72\sigma_1 + 0.28\sigma_R)$$

The effect of 6-substitution appeared to be almost completely inductive. Dissociation constants of 4-substituted pyrimidines correlated best with σ_p constants, but 2-substituted examples again had a greater inductive component (69JOC821).

There are instances where theoretical and experimental charge distributions are found to correspond well with protonation behavior, as demonstrated by electron spectroscopy for chemical analysis (ESCA) spectral and complete neglect of differential overlap (CNDO/2) theoretical results. Respective excess electron densities determined by these two methods are uracil N-3 (−0.24, −0.23), uracil N-1 (−0.21, −0.18), 5-fluorouracil N-3 (−0.19, −0.24), 5-fluorouracil N-1 (−0.18, −0.18) (78CJC1555).

When there is an N-oxide function present in an azine, another site becomes available for proton attack. Although pyridazine N-oxides often react at the free nitrogen, pyrimidine oxides frequently form the hydroxy salts (83CHE1012).

In parallel with the protonation behavior, pyridazines should undergo N-

alkylation and N-acylation rather more readily than the other diazines and triazines. Indeed, pyridazines show greater nucleophilic reactivity than that predicted from protonation studies *vide infra*.

III. Alkylation

Only recently have attempts been made to obtain quantitative data describing the relative reactivities of the azines toward alkylating agents. The assumption that virtually all such quaternizations can be classified as S_N2 with respect to the participating carbon center is probably justified (78AHC71). Products are usually formed irreversibly and where more than one product is possible, their ratios are independent of time.

A variety of alkylating agents have been used successfully to N-alkylate azines: alkyl halides (53JCS1646; 56JOC764; 56JOC812; 65AJC199; 71JA5475; 73ACS383; 76JCS(P1)1424; 77LA1969; 78AJC389; 78JOC3362; 78TL1663; 79ACS(B)515; 79H203; 80BSF(2)559; 81ACS(B)69; 82ACS(B)15; 82JHC373; 85AJC1809; 85JHC1077; 86ACS(B)381), sometimes phase-transfer catalysis conditions (78TL1663; 81ACS(B)69; 81S631; 82JHC373), dialkyl sulfates (78AJC389; 78JHC105; 78TL1663; 80BSF(2)559), trialkyl phosphates (78TL1663; 80BCJ277), diazomethane (78JHC105; 80BSF(2)559; 81ACS(B)69; 85AJC1809), dimethylformamide dialkyl acetals (81AJC1729; 81S118; 82ACS(B)15), vinyl ethers (80CHE1176), vinyl acetate (80CHE299), ethylene carbonate (78CHE562), ethylene oxide (80CHE299), and glycosyl halides (79JHC353; 79JHC1049; 84TL5061). In cases where the azines bear tautomerizable substituents, exocyclic alkylation can become a competing reaction and the product may be controlled to some extent by the nature of the alkylating agent.

From the large volume of kinetic data available for substituted pyridines, benzologues, and some diazines, Zoltewicz and Deady (71JA5475; 72JA2765; 72T1983) have calculated a series of substituent rate factors that can be used quite successfully to predict relative rates of N-methylation of pyridine derivatives with methyl iodide in dimethyl sulfoxide (DMSO) at 23°C. Among these logarithmic factors are those for *ortho* (−0.60), *meta* (−1.36), and *para* (−0.45) annular nitrogens, permitting predictions to be extended to the methylation of azines. That the substituent constants are affected by steric factors is exemplified by the ratio of rate coefficients (0.47:0.23:0.054) for the alkylation of 2-methylpyridine by methyl, ethyl, and isopropyl iodides in nitrobenzene at 25°C (56JCS1248; 59MI1). In addition, steric factors are not directly additive [e.g., two *ortho* methyl groups have a greater substituent constant (−1.64) than twice the constant (−0.42) for each methyl group

alone]. Solvent and tautomeric effects can also complicate matters. The assumption has to be made that ρ values for different classes of compounds are similar (e.g., the ratio of reaction constants for methylation of monosubstituted pyrazines and pyridines is 1.06 (71JA5475)).

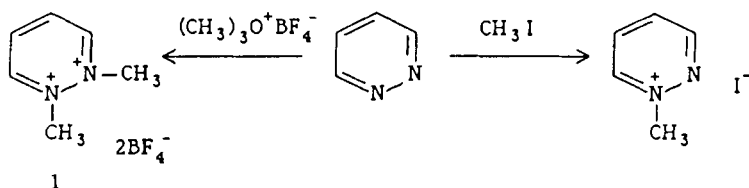
The aza substituent constants (*vide supra*) reflect the fact that electron-withdrawing annular nitrogens decrease the reactivity of any other ring nitrogen in the order *ortho* \ll *meta* $<$ *para*. For this reason, pyrazines should quaternize more readily than pyrimidines and pyridazines, and all three diazines should react faster than triazines. When the diazines are included in a Hammett plot for the methylation of substituted pyridines ($\rho = -2.3$), the positive deviations showed that they were all more reactive than indicated by their pK_a values. Relative rates compared with pyridine were pyridazine, 0.25; pyrimidine, 0.044; and pyrazine, 0.036 (72JA2765). Pyridazine in particular appears to be much more reactive than one would expect. (See Section III, A below).

It proved possible to estimate the reactivity of a particular nitrogen in an azine ring, hence the ratio of isomeric quaternary salts which would be expected, and the approximate second-order rate constant for methylation of the azine. The method is, however, better suited to prediction of product ratios than rate coefficients, since steric effects largely cancel in the former. Examples of the predictive value of this approach will be included with the discussion of the individual azines.

Complications can arise when tautomerizable substituents are present. With the sole exception of the 5-position of pyrimidine, all nuclear positions of azines bearing amino, hydroxyl, and thiol groups are capable of tautomerism, making possible S_E2 , S_E2' , and S_E2cB mechanisms of alkylation. The overall reaction course will be controlled by the nature of the intermediate and the reaction conditions, but the frequent observation of both nuclear and exocyclic alkylation makes the mechanism difficult to discern. Generally, hydroxy- and thioazines react largely as the oxo and thione tautomers, but amino compounds seldom react as the imino form.

A. PYRIDAZINES

The observation that pyridazine reacts vigorously with alkyl halides (56JOC764; 56JOC812; 72JA2765)—it can even form a diquat (**1**) when fused with oxonium reagents (72JOC2259)—has been explained in terms of neighboring group participation by one nitrogen in the transition state for quaternization of the other, as suggested for 1,8-naphthyridine (69CC56). This rate enhancement (or α -effect), characterized by positive deviations from a Brønsted plot, is a threefold increase over that expected from the pK_a value. It



SCHEME 1

is known that electronic effects of unshared electron pairs on adjacent (and also on more widely spaced) nitrogens can be transmitted through space and through bonds. Similar rate enhancements are apparent in N-acylation reactions of pyridazines, and these are discussed further in Section IV. From qualitative comparisons of the ease of methiodide formation, an appropriate order of relative activation ($\text{CH}_3 > \text{H} > \text{Cl} > \text{SCH}_3 > \text{Ph} > \text{OCH}_3$) of pyridazine to quaternization was found (72T1983).

In the alkylpyridazines, quaternization can give mixtures of isomeric salts. With methyl iodide, 4-methylpyridazine formed equal amounts of 1,4- and 1,5-salts (66JCS(B)867; 73ACS383), while the 3-methyl isomer gave a 2.6:1 mixture of the 1,3- and 1,6-dimethyl iodides (66JCS(B)867; 72T1983; 73ACS383). For the latter substrate, the calculated isomer ratio based on Zoltewicz's substituent factors is 4.3:1 (72T1983).

Lund (67ACS1067) devised an earlier list of substituent factors specifically for the calculation of ratios of pyridazine methiodide isomers (Table II). These differ from the more general factors in that they represent differences between *ortho* and *meta* rate factors rather than being factors for individual ring positions. The pyridazine substituent factors, K_s , rely on the assumption that the rate of methylation of a pyridazine nitrogen is almost entirely dependent on the adjacent substituent. Hence, the isomer percentage can be calculated for methylation of a 3-X-6-Y-substituted pyridazine from $100 K_s^Y / (K_s^Y + K_s^X)$; K_s will have different values for different steric effects (e.g., arising from a change in alkylating agent). Isomer ratios have been quoted for many substituted pyridazines (59JCS3789; 67ACS1067; 71RRC1107; 76JCS(P1)1424; 76MI1; 76RRC717), but values obtained gravimetrically will not be very accurate. Table II lists product ratios determined by NMR methods along with the predicted ratios, which show generally good agreement. Those examples for which the calculated ratios vary considerably from the experimental results reflect the problem that both alkylation sites are subject to steric effects which will depend on the sizes of the substituents. A measure of these steric effects in 3-methyl-6-R-substituted pyridazines is given by $\log k/k_0$, where k_0 is the rate of methylation of 3,6-dimethylpyridazine. Typical examples are (R, percentage N-2-methylation in acetonitrile, $\log k/k_0$

TABLE II
QUATERNIZATION OF SUBSTITUTED PYRIDAZINES WITH METHYL IODIDE

$K_s Y^a$	X	Y	Ratio (%) of 2:3		
			Expt. ^{a,b}	Calculated ^c	Calculated ^a
1.00	Me	H	72/28	81/19	72/28
0.38	Me	Me	50/50	50/50	50/50
0.10	Me	Cl	21/79	11/89	21/79
0.105	Me	Br	23/77	12/88	23/77
0.30	Me	NH ₂	45/55	58/42	44/56
0.027	Me	NHAc	11/89	10/90	7/93
0.30	Cl	NH ₂	69/31	92/8	75/25
0.025	H	Ph	8/29		6/94
0.25	Me	Ph	3/97		3/97

^a 67ACS1067.^b 73ACS383.^c 72T1983.

given) Me, 50, 0; Et, 65, -0.27; *i*Pr, 81.5, -0.64; *t*Bu, >99.5, > -2.30 (72TL3857).

The steric effect, however, depends on the geometry of the heterocycle, the nature of the alkylating agent, the solvent, and the temperature, and so the effective volume of any group may not be constant. Thus, although 3- and 6-phenyl groups are usually coplanar with the hetero ring, a 4-substituent can exert sufficient steric hindrance to force them out of plane. For this reason, 3,4,6-triphenylpyridazine methylates mainly at N-2; the 3-phenyl group is twisted 90° out of the plane of the pyridazine ring and has a smaller effective volume. A further illustration of this conformational dependence of the steric effects of phenyl is that 6-methyl-3-phenylpyridazine is methylated 92% at N-1 and 8% at N-2, but the corresponding compound with a 4-*t*-butyl group gives an N-1:N-2 ratio of 38:62. In the absence of 3-substituents, a variety of alkyl groups at C-4 showed only minimal steric effects; product ratios remained close to 1:1 (73ACS383).

The tendency for larger alkylating agents to attack the less hindered nitrogen is demonstrated by the orientation of quaternization in a series of 3-methyl-6-*R*-substituted pyridazines. The percentages of N-1 substitution observed using methyl, ethyl, and isopropyl iodides in turn were 72, 80, and 90

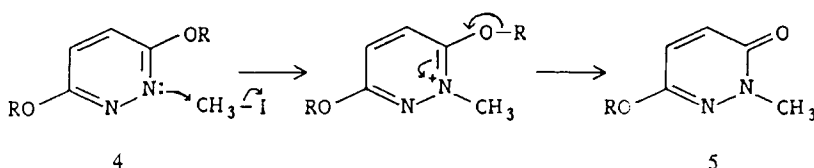
for $R = H$; 21, 31, and 51 for $R = Cl$; and 30, 51, and 64 for $R = I$ (67ACS1067).

Sometimes the effects of solvent may not be very great. 3-*t*-Butyl-6-dimethylaminopyridazine reacted with methyl iodide in acetonitrile to give a 63:37 ratio of 1- and 2-methiodides. The results in hexane, benzene, carbon tetrachloride, and acetone were similar, and only in ethers [dimethoxy-methane, 79:21; tetrahydrofuran (THF), 84:16] did the product ratios vary to any extent, perhaps because the methylating agent in ethers is an oxonium salt (73ACS383).

Inductive effects can sometimes influence product orientation. Whereas 3-methyl-6-methoxypyridazine methylates only at N-2, the 6-chloro- and 6-iodo analogues gave 21 and 22%, respectively, of the N-1 product (67ACS1067).

In a study of the influence of amino substituents on pyridazine methylation, Barlin (76JCS(P1)1424) has shown that a 3-amino group directs most attack toward N-1 (N-1:N-2 = 3:1), and 4-amino and 4-dimethylamino substituents gave 2:1 (76JCS(P1)1424) and 3:1 (73ACS383) ratios, respectively, of the 1- and 2-methiodides. Both 3,4- and 3,5-diamino derivatives showed similar trends, giving close to 100% 1-methylation. Apparently, the 4-amino groups are exerting +M effects. Generally, however, product, orientation is much more influenced by steric than by electronic factors, and contradictory results reported in the earlier literature are probably a consequence of such alkylations of aminopyridazines being reversible. If an annular nitrogen is hindered, attack can take place preferentially at an exocyclic amino or alkylamino function. Since the resulting quaternary salt may have higher energy than the ring-alkylated product (in which the amino group may help stabilize the cation), a rise in temperature could induce Dimroth rearrangement to the thermodynamically more stable isomer.

When 3,6-dialkoxypyridazines (**4**) are heated with a variety of catalysts (e.g., mineral acids, *p*-toluene sulfonic acid, Lewis acids), rearrangement occurs to give the 3-alkoxy-1-alkylpyridazin-6(1*H*)-ones (**5**). Thus N-methylated pyridazinones can be prepared by treatment of 3,6-dialkoxypyridazines with methyl iodide or dimethyl sulfate (84MI2), the reaction mechanism presumably involving an intermediate quaternary pyridazinium salt.



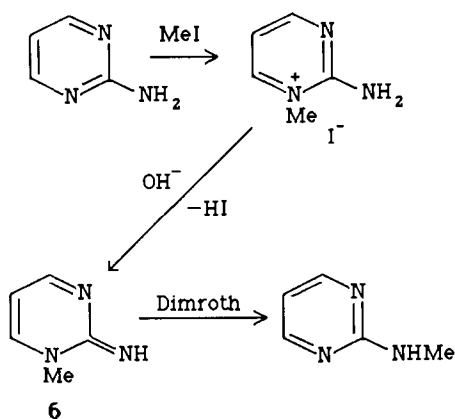
SCHEME 2

Few reliable measurements exist for N- and O-alkyl product ratios in the 3(2*H*)-pyridazinones. It is known that in basic medium the anionic species methylate almost exclusively at N-2 with methyl iodide, dimethyl sulfate, α -halo acids, and α -halo esters (21CB1035; 50JCS3500; 58CPB722; 60JCS3371; 71BSF1752; 78AJC389; 81S631), but some methoxy products are formed with ethereal diazomethane (01CB3257; 49AG397; 79JOC3053) and with bulky alkylating agents. For example, pyridazin-3(2*H*)-one is benzylated to give a 2:1 mixture of the N- and O-benzyl isomers, while ethoxycarbomethylation with diazoacetic ester gives a 1:10 ratio of N- and O-substituted derivatives (84MI2). 4(1*H*)-Pyridazinones can be alkylated at either nitrogen, depending on other ring substituents (56HCA1755; 58AC(R)1316; 58AG5; 76TL521). With 3,6-dihydropyridazine (maleic acid hydrazide), O-alkylation competes even more effectively (49AG397; 54HCA837; 82JOU1365), and this may be followed by Hilbert—Johnson rearrangement to the N-alkyl isomers (65CCC3744). Thiol groups are even more subject to alkylation than hydroxyl (62JCS3129; 64BCJ1107; 77JCS(P1)1038; 78AJC389; 81AJC1729). Thus, 6-chloropyridazine-3(2*H*)-thione is methylated by dimethylformamide dimethylacetal initially at the sulfur atom (81AJC1729), and methyl iodide in basic medium converts pyridazine-3,4,6-trithiol into the tri-S-methyl derivative (78AJC389). 4,6-Diaminopyridazin-3(2*H*)-thione is methylated in basic medium first on the sulfur, but with excess methyl iodide some 1-methyl product was formed and confirmed by a crystal structure analysis (81H9). 3-Methylpyridazine 1-oxides are methylated only on the oxygen function (66YZ81; 67TL113).

B. PYRIMIDINES

Simple alkylation of pyrimidines with non tautomerizable substituents are largely controlled by steric factors. Thus, 4-*t*-butyl-6-methylpyrimidine is converted by benzyl bromide in toluene exclusively into the 1-benzyl product (82JHC373). Although pyrimidines are less readily alkylated than pyridazines, diquats are still accessible through the use of oxonium alkylating agents; steric effects of flanking methyl groups can reduce yields (72JOC2259).

Kinetic data for substituted pyrimidines indicate that an *ortho* amino group is always more activating than methyl or chloro in the same position (72T1983; 78AHC71), and, in contrast to an earlier view based on preparative experiments (64AHC1), the reactivities of aminopyrimidines lie in the order 4 > 5 > 2. In cases where tautomerism cannot be a complication [5-amino-(51JCS1565) and 2- and 4-dimethylaminopyrimidines (65AJC199)], the 1-methylpyrimidinium iodides formed readily, but both annular and exocyclic alkylation were found with 2-aminopyrimidines (55JCS4035; 71JCS(C)425;



SCHEME 3

73JHC275). A high proportion of so-called exocyclic alkylation must be a consequence of Dimroth rearrangement caused by alkaline workup. On treatment with cold alkali, the methiodides of pyrimidin-2- or -4-amines form anhydro bases (**6**), which are unstable and frequently undergo such Dimroth rearrangements (68MI1; 70HC284; 84MI3) (Scheme 3). 4-Aminopyrimidines are quaternized mainly at N-1 (55JCS1853; 55JCS4035; 65AJC199) due to the +M effect, and 2,4-diamino-6-chloropyrimidine gives both N-1 and N-3 salts (81CC1224). The influences of other substituents in aminopyrimidines are mainly manifested through their inductive and steric effects (55JCS1853; 60JCS1978; 63JCS3535; 65JCS5542, 66JCS(C)164; 67JCS(C)1922).

Considerable data are available for alkylations of 2-, 4-, and 6-hydroxypyrimidines, in which N-methylation generally predominates, but comparisons of yields from the literature are invalidated by the wide variety of reaction conditions employed.

With 2- (66JOC3969) and 4-hydroxy compounds (70JOC2512; 80BSF(2)559; 85JHC1077; 86ACS(B)381), the reaction rates are largely governed by the nature of the alkylating agent and steric effects of adjacent substituents, although electronic effects can also influence matters. For example, 4-methoxycarbonyl-5-chloropyrimidin-2(1*H*)-one is methylated by methyl iodide in sodium methoxide principally at the 1-position (79ACS(B)150). The nature of any intermediate cation, the leaving group, and changes in reaction temperature have little effect on product regiochemistry. Thus, product distribution does not seem to be related to any $\text{S}_{\text{N}}1$ – $\text{S}_{\text{N}}2$ gradation in mechanism.

The anionic form of 5-chloropyrimidin-2(1*H*)-one, particularly under phase-transfer conditions, was selectively methylated and benzylated at

nitrogen. Under the same conditions only low yields of the N-butyl product were obtained, while polymerization prevented any formation of the corresponding allyl and propargyl derivatives (79ACS(B)150; 81ACS(B)69). With α -haloaryl sulfides, 5-halogenopyrimidin-2(1*H*)-ones mainly gave N-alkylated products, especially in the presence of tertiary amine bases and in solvents of low dielectric constant (85JHC1077). Other soft electrophiles (e.g., methyl iodide, benzyl bromide) gave N-alkyl products (81ACS(B)69), but with the much harder electrophiles (α -chloroalkyl ethers), the anion of a 5-halogenopyrimidin-2(1*H*)-one was preferentially O-alkylated at the harder part of the ambident anion (83ACS(B)345). Second-order kinetics have been firmly established in the reaction of isopropyl bromide with 2-hydroxy-4-methylthiopyrimidine (66JOC3969) and for alkylations of 2-substituted-4-hydroxypyrimidines (70JOC2512). For the latter reactions, k_2 decreases as the size of the alkylating agent increases (Table III).

TABLE III
SECOND-ORDER RATE COEFFICIENTS^a FOR
ALKYLATION OF SODIUM SALTS OF 2-SUBSTITUTED-4-
HYDROXYPYRIMIDINES^b IN METHANOL^c

Alkylating agent	2-Substituents		<i>T</i> (°C)
	H	Me	
MeI	3.34	1.84	54
EtI	2.28	—	54
EtI	4.95	3.44	94
<i>i</i> PrI	1.70	1.37	94

^a $10^3 k_2$ (dm³ mol⁻¹ sec⁻¹).

^b 0.45 *M*.

^c 70JOC2512.

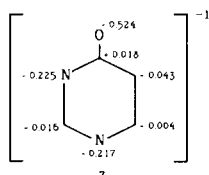
TABLE IV
EFFECT OF ALKYLATING AGENT ON ISOMER
RATIOS IN 2-PYRIMIDINONE.^a

Alkyl iodide ^b	% complete	Product distribution (%)	
		<i>N</i>	<i>O</i>
Me	83	98	2
Et	99	84	16
<i>i</i> Pr	98	67	33
PhCH ₂	96	98	2

^a Reaction as sodium salts (66JOC3969).

^b Chlorides and bromides gave essentially the same results.

A study of the effects of change in alkyl halide on isomeric product ratios for alkylations of substituted 2-hydroxypyrimidines demonstrates that changes in those ratios can be attributed to overall kinetic control (Table IV). Since N-alkylation is sterically more demanding than O-alkylation, e.g., adjacent phenyl groups induce preferential O-alkylation of 2-hydroxypyrimidines (84CHE1185), then the rate of reaction at nitrogen will decrease relative to that at oxygen (which remains fairly constant) as the bulk of the alkylating reagent increases [cf. pyridazines (*vide supra*). In the absence of steric effects from substituents, the preference for N-alkylation is consistent with the higher polarizability of the nitrogen atom, and with the greater localization of positive charge on it in the product.



There can be considerable solvent dependence of rates and regiochemistry of alkylation in 4-hydroxypyrimidines (70JOC2512; 80BSF(2)559) (Table V). As the solvent decreases in dielectric constant, the N-3:N-1 ratio decreases sharply. The ground-state distribution of the isolated ion (7) of 4-hydroxypyrimidine has 75% of the charge distributed between N-3 and the oxygen atom, accounting for the high proportion of attack at N-3 in solvents such as dimethylformamide (DMF). Solvent changes seem to have less effect

TABLE V
EFFECTS OF SOLVENT ON REGIOCHEMISTRY OF
ALKYLATION OF 4-PYRIMIDINONES

Substrate	Solvent	Time (hr)	% Yield	Product ratio		
				N-1	N-3	O
4-OH-2-Me ^a	DMF	17	82	21	50	29
	MeOH	13	80	16	59	25
	<i>i</i> PrOH	5	84	36	47	17
	EtOAc	24	23	90	5	5
4-OH-5-Ar ^{b,c}	DMF	17	93	—	100	—
	MeOH	24	87	38	62	—
	EtOAc	48	88	66	34	—
	THF	48	89	73	27	—

^a Ethylation of sodium salt with ethyl bromide at 40°C (70JOC2512).

^b Ar, *p*-nitrophenyl.

^c Methylation with methyl iodide (80BSF(2)559).

on the rate of O-alkylation. Variation of the 5-aryl substituents had only a minor influence on the site of alkylation through the electronic effects of *p*-substituents (80BSF(2)559).

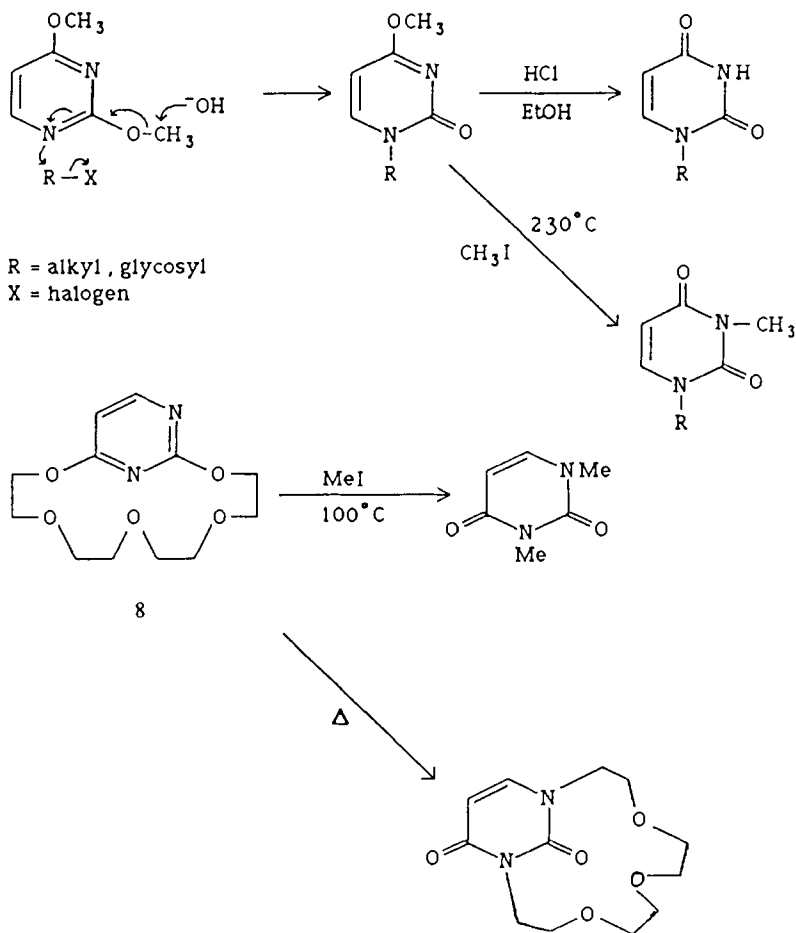
Although the use of silver salts in benzene has been recommended as providing a high proportion of O-alkyl product, yields are usually low (70JOC2512), and the product distribution is not appreciably different from sodium salt reactions (66JOC3969). However, diazomethane gives considerable methoxy product as usual (54JCS3832; 55JCS211; 66AJC2321; 66BSF5; 71JOC848; 80BSF(2)559), and trimethylsilylation occurs almost exclusively at oxygen (64CPB352; 64ZC303; 65AG(E)417; 65JHC313; 73BSF2709).

Cytosine [4-aminopyrimidin-2(1*H*)-one] can alkylate largely on N-3 (62JCS1348) or N-1 (78JOC1593), depending on the reagent, but the dimethylamino analogue gave both N-methyl salts as did isocytosine (65AJC199). With trialkyl phosphates in DMF (80BCJ277), the major product was the 1,3-dialkylated cytosine, but with ethylene carbonate (78CHE562) or trimethyloxonium hydroxide (78JOC1593) the sole product in >85% yield was the 1-alkylated cytosine. Dimethylformamide dimethylacetal is a specific methylating agent for N-1 of cytosine (81S118). Most 4-amino-6-hydroxypyrimidines are methylated preferentially at N-1 (58LA163; 58LA173; 61JCS1298; 62LA149).

Uracil and its N-unsubstituted derivatives generally form 1,3-dialkyl products under a wide variety of conditions (53JA5758; 59JCS50; 66CB2380; 71JOC848; 73JCS(P1)391; 77BCJ1510; 78CHE562, 78JOC1593; 81AJC1792), including phase-transfer catalysis with the dianions (78TL1663; 78TL3203; 81ACS(B)69; 81JHC339). Larger alkyl groups display a preference for the less hindered nitrogen, N-1 (73JCS(P1)391; 77BCJ1510; 78TL3203), and some O-alkylation occurs with diazomethane especially with DMF as solvent. A 5-methyl group has little steric effect on adjacent O-alkylation (71JOC848).

In 1-substituted uracils, competition for further alkylation can only be between N-3 and oxygen. In most instances, particularly for reactions of the sodium salts, N-alkylation is favored (72BAU352), but hindered alkyl halides and diazomethane again give a proportion of O-alkyl products (66CB2380; 71JOC848). *p*-Methoxy groups are frequently cleaved in these reactions (30JA2001; 65AJC199; 68JA1678), and the Hilbert-Johnson reaction leading to the synthesis of N-glycosides by fusion of protected glycosyl halides with dihydroxypyrimidines has become well established in nucleoside synthesis (Scheme 4) (47JCS1052; 67AHC115; 68JA1678; 73CPB1510; 73RCR494; 81AJC1157). An interesting example of this reaction involving a pyrimidine-substituted crown ether (8) has been reported (Scheme 4) (78JOC3362).

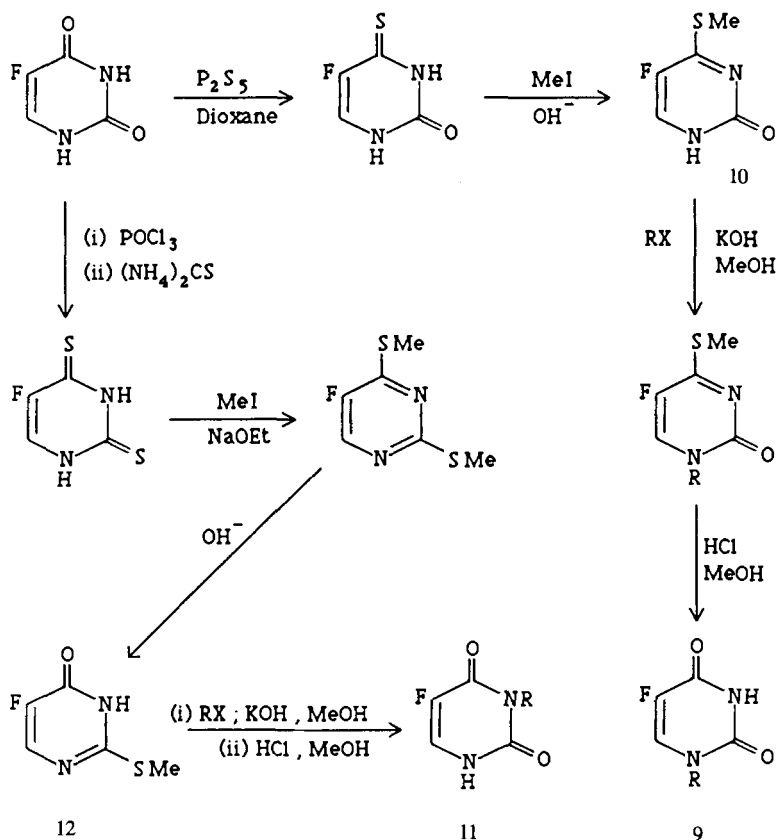
Alkylthio groups are not cleaved in this manner (59JCS3789; 64AHC1).



SCHEME 4

This has been utilized in the regioselective alkylation of 5-fluorouracils (79ACS(B)515), in which the N-1-derivative (9) was prepared via the 4-methylthiol (10) and the other isomer (11) via the 2-methylthiol (12) (Scheme 5). The regioselectivity is achieved by making use of the activating effect of a sulfide group, which can be reconverted into an oxo function after alkylation. A more recent method (84H527) makes use of the (octylthio)carbonyl protecting group.

Whereas free thiol or thione functions are readily alkylated, especially in basic media (62JCS3124), 2-alkylthiouracils normally alkylate preferentially at N-3 (82ACS(B)15). With dimethylformamide dimethylacetal, significant



SCHEME 5

O-methylation occurred, but the corresponding dibenzylacetal was fairly unreactive and gave only O-benzylated product. With *N,N'*-dicyclohexyl-*O*-alkylisoureas, both *O*- and *N*-3-alkylation occurred with steric factors again favoring *O*-alkylation (with the benzylisourea); alkyl halides in methanolic KOH were rather less specific, giving mixtures of the three possible isomers in which the *N*-1- and *N*-3-alkylated products dominated (82ACS(B)15).

It is interesting to note that 5-nitrouracil can be alkylated in a stepwise fashion, initially at *N*-1 (02LA160; 25LA203; 65UKZ215). The selective *N*-1-attack is on the monoanion (*H*-1 is more acidic than *H*-3), but in the dianionic form *N*-3 is more basic, and presumably more nucleophilic, than *N*-1. Hence, in strong base, *N*-3 is attacked exclusively (70JHC735).

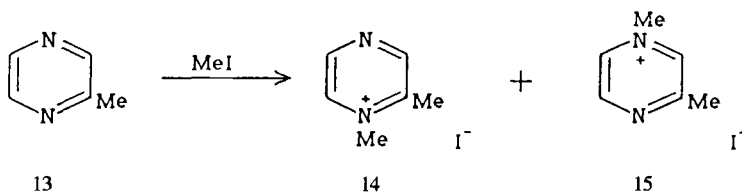
Barbituric acid and derivatives resemble uracils in their preference for

N-alkylation with most reagents (57BBA295; 60RCR437; 66AJC2321; 70AC347; 76AJC1769; 78AJC2517), although, again, larger alkylating agents are responsible for increasing amounts of O-alkyl products (78AJC2517). Direct alkylation of barbituric acid, preferentially occurs at C-5 rather than in the 1- or 3-positions (85AHC229). Diazomethane, however, converted barbituric acid into 6-methoxy-1-methyluracil (72CJC880), and the alkylation of 1- or 5-monosubstituted barbiturates gives rise to products of both O- and N-alkylation (72CJC880; 76JPS288; 80MI1). In 5,5-disubstituted barbiturates, N-methylation is the predominant reaction (72TL3921; 75AJC2265; 76AJC1769). Pyrimidine N-oxides are mainly O-alkylated (81CHE1105).

C. PYRAZINES

The parent base and its alkyl derivatives are readily monoalkylated by alkyl halides, and mono- and dialkylated by oxonium agents (64AHC1; 72AHC99; 72JOC2259; 85H2299), with the alkyl groups exerting mainly steric effects. 2-Methylpyrazine (**13**) gives a 1:4 mixture of the 1- (**14**) and 4-methiodides (**15**) (71JA5475) (Scheme 6), close to the predicted ratio of 19:81 (72T1983). A report of methylation in acetone has described a 1:1 ratio of 1,2- and 1,3-dimethyl salts from 2-methylpyrazine, and from 2,6-dimethylpyrazine a 1:9 ratio of 1,2,6- and 1,3,5-quaternary salts (85H2299). Since pyrazines are about 28 times less reactive than pyridines towards methylation with methyl iodide (at 20°C in DMSO), substituent effects should be greater (71JA5475). The total relative rates of methylation of 2-substituted pyrazines relative to pyrazine have been determined by a kinetic competition method giving the k_{rel} values NH_2 , 8.8; Me, 2.0; OMe, 1.05; CONH_2 , 0.53; F, 0.16; Cl, 0.15.

Correction to allow for isomeric products ($k_{\text{isomer}} - k_{\text{total}} \times \% \text{ isomer}$) changes k_{rel} to 1.65 for 2-methylpyrazine, which forms the 1,3-dimethyl salt. A linear free-energy relationship was found involving rate coefficients for the formation of 3-substituted pyridinium and pyrazinium ions, with the slope of correlation (1.06) demonstrating the slightly larger substituent effects in the



SCHEME 6

less reactive pyrazines, in which the unreactive N-1 acts as a constant electron-withdrawing substituent. The correlation can be used to provide unambiguous proof of the identities of isomeric methylation products (71JA5475).

When an amino group is present, alkylation still occurs at both annular nitrogen atoms (71JA5475); at room temperature, methyl iodide in DMSO converts 2-aminopyrazine into a 26:74 mixture of 1- and 4-methiodides [predicted (72T1983) ratio 24:76], a result not greatly different from 2-methylpyrazine. The observation that 2-aminopyrazine is alkylated mainly at N-4 but protonated at N-1 (60JCS242) is explicable in terms of the properties of model aminopyridine compounds. While 2-aminopyridine is more basic than the 3-amino isomer, the steric effect makes it less prone to quaternization (72JOC603). Indeed, steric factors are responsible for most 2-substituted pyrazines being alkylated at N-4. That Dimroth rearrangement is possible in the series is confirmed by the isolation of some exocyclic N-aryl product when 2-aminopyrazine is treated with picryl halides (73JHC275).

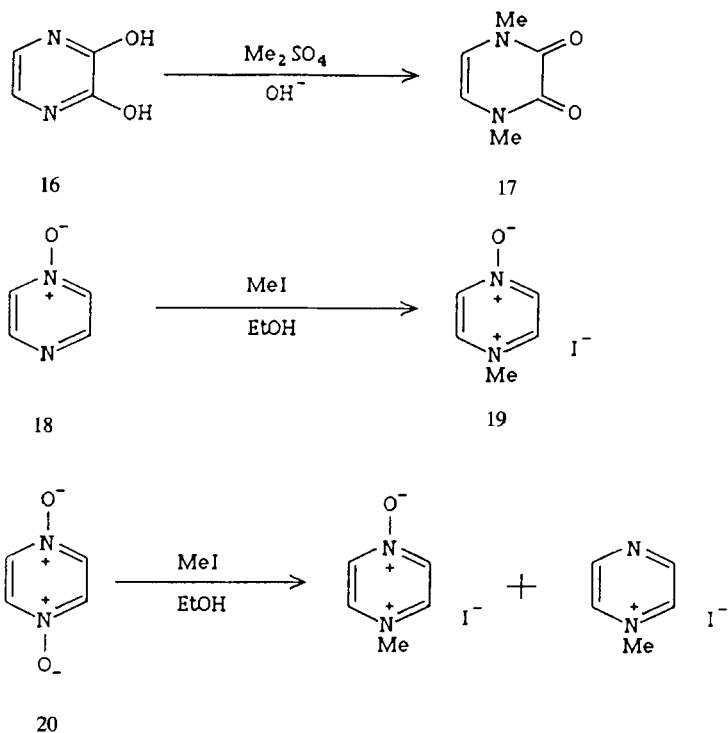
With dimethyl sulfate (60JCS242) or diazomethane (47JBC341), 2-hydroxypyrazine gave 1-methylpyrazin-2(1*H*)-one, although no attempt was made to detect O-methyl products. Certainly 2-hydroxy-5-methoxypyrazine is largely O-methylated by diazomethane. Most alkylating agents, though, attack the nitrogen adjacent to the oxo function. 2,3-Dihydroxypyrazine (**16**) gave the 1,4-dimethyl product (**17**) with alkaline dimethyl sulfate, but a mixture of N, N-, N,O- and O,O-dimethyl products with diazomethane, and mostly O-methyl compounds when the hindered 5,6-diphenyl compound was methylated (65JCS6681).

Ethanollic methyl iodide converted pyrazine 1-oxide (**18**) into the 4-methyl salt (**19**). There was no sign of O-methylation. With the 1,4-dioxide (**20**), the same reagent reduced off oxygen functionality (Scheme 7) (85H2299). Both methyl iodide and benzyl chloride gave the 4-quaternized product with 2,5-dimethylpyrazine 1-oxide; no O-alkylation was observed (58JOC1603), although it sometimes occurs (78CPB2046).

D. TRIAZINES

1,2,3-Triazine is attacked by methyl iodide, ethyl chloroformate, and picryl chloride at N-2 (79CB1514; 79CB1535; 84H674). Similar treatment of 4,5,6-triphenyl-1,2,3-triazine 2-oxide gave only the 1-methyl salt; no methoxy product was identified (84H674).

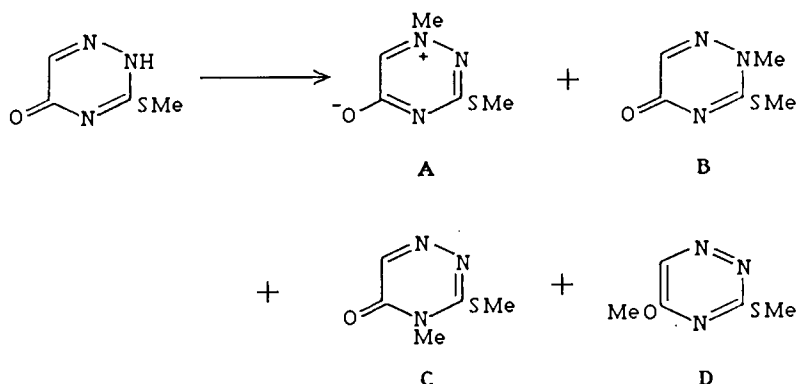
A little more is known about the quaternization of substituted 1,2,4-triazines, but alkylation sites are frequently uncertain (63JCS1628). The observation that 1-alkyl salts are red while the 2-alkyltriazinium iodides are colorless is of some assistance. The isolation of the 3-dimethylamino



SCHEME 7

compound from the methylation of 3-amino-1,2,4-triazine in alkaline medium was probably a result of a Dimroth rearrangement induced by the strongly electron-withdrawing nature of the third aza-substituent (61MI1). More recent examination of this reaction in DMSO showed the presence of two N-methyl products in the ratio 1.6:1, and a trace of a third isomer. The major product (61%) diminished in concentration over a period of time, further suggesting rearrangement. The predicted product ratio is 18 (N-1):7 (N-2):1 (N-4) (i.e., 69% of the 1-methyl salt), but these calculations do not allow for the possibility of Dimroth rearrangement (72T1983).

The regiochemistry of methylation of 1,2,4-triazin-5(2*H*)-ones is affected profoundly by the reagent. With alkaline methyl iodide or dimethyl sulfate, the N-2:N-4 ratio was 2–3:1 (72BSF1511; 73BSF2126; 74T3171; 83H51), but diazomethane methylates the oxygen as well (60CB187; 73BSF2126; 85AJC1809). With a stoichiometric amount of diazomethane, N-methylation still predominates; with excess reagent, N-methylation is preferred in polar solvents, but O-methylation increases as the solvent polarity decreases



$$\text{CH}_2\text{N}_2 : (\text{A}) : (\text{B}) : (\text{C}) : (\text{D}) = 19 : 23 : 28 : 30$$

$$\text{MeI} / \text{NaOH} : (\text{A}) : (\text{B}) : (\text{C}) = 28 : 54 : 18$$

$$\text{MeI} / \text{NaOMe} : (\text{B}) : (\text{C}) = 82 : 18$$

SCHEME 8. Isomer ratios from methylation of 3-methylthio-1,2,4-triazin-5(2H)-one, determined by integration of ^1H -NMR spectra.

(60CB187; 73BSF2126). Electron donors at C-6 increase the proportion of 2-methylation, while a methylmercapto group at C-3 has been reported to direct much of the attack toward N-4 (61CCC986; 62CCC1898; 72BSF1511; 85AJC1809). One paper (85AJC1809) describes the use of ^{13}C -NMR to determine the methylation products of 3-methylthio-1,2,4-triazin-5(2H)-one using diazomethane or methyl iodide in sodium hydroxide or sodium methoxide. Ratios of the four possible products (shown in Scheme 8) were obtained by integration of the ^1H -NMR spectra. As has been found elsewhere, diazomethane gives a considerable proportion of exocyclic O-methylation, while the basic solutions of methyl iodide promote attack on the triazine anion, giving mainly N-methylation. When there are two hydroxy groups present, as in 1,2,4-triazin-3,5(2H,4H)-dione (6-azauracil), most alkylating agents in basic medium give mainly 2- and 4-monoalkyl derivatives. Similar reaction conditions usually lead to N,N-dialkyluracils, and this demonstrates the deactivating effect of the extra annular nitrogen (61CCC974; 62CCC1572; 65CCC3890; 78HC189). More vigorous conditions ultimately lead to the 2,4-dialkyl products (78HC189). Even diazomethane gives only a minor amount of O-methylation (61CCC974) as it does with uracil (*vide supra*). Hilbert-Johnson reactions occur exclusively at N-2, obviating any need for protecting groups (65JHC495; 67JHC291; 73JOC3277; 75RRC1287).

With 1, 2, 4-triazine thiols, S-alkylation always predominates (61CCC986; 62CCC1898; 70RRC1409; 72BSF1511; 76JCS(P1)2521), as with analogous 1,3,5-triazines (66JCS(C)909; 71CB1580; 71CB1606).

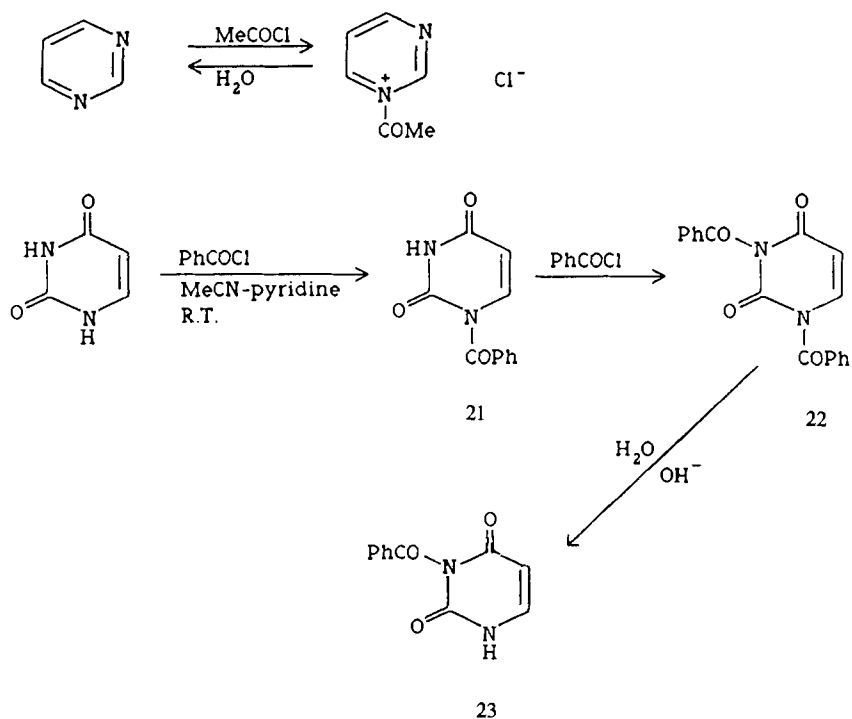
Dialkylhalo-1,3,5-triazines self-quaternize (65JOC702), methoxy derivatives are demethylated (30JA2001), and amino compounds (e.g., melamine) undergo Dimroth rearrangement (61HC681) under alkylation regimes. With most reagents, 1,3,5-triazin-2,4(1*H*, 3*H*)-dione gave a mixture of 1-methyl- and di-*N*-methyl derivatives (21CB5448; 26JPR138), but in polar solvents diazomethane formed appreciable methoxy product (63CCC2365) in contrast to uracil and 6-azauracil. 4-Amino-1,3,5-triazin-2-(1*H*)-one and its 6-alkyl derivatives gave the 1,3-dimethyl (87%) and 3-methyl (2.5%) products when treated with methyl iodide in DMF (67CCC4271), while cyanuric acid was able to be *N*-alkylated with benzyl chloride (05CB1005).

IV. Acylation

Annular *N*-acylations are not at all common, especially among the fully aromatic azines. Any acyl groups so introduced can act as labile blocking groups, frequently so labile that they are powerful acylating agents (58JBC185; 62HC1; 72JHC1423; 73KG1132; 77BCJ2406; 78CHE227). The *N*-acyl salts are very readily hydrolyzed (Scheme 9).

The rates of acetylation of diazines by *p*-nitrophenyl acetate (72JA2765) or 2,4-dinitrophenyl acetate (72CC522; 72TL189) in aqueous solution give a sensitive measure of the relative nucleophilicities of diazine ring nitrogens (the diazines act as nucleophilic catalysts of ester hydrolysis), especially with reference to the anomalous alkylation reactivity of pyridazine (*vide supra*). The average second-order rate constants for the reactions of pyridine and pyridazine with *p*-nitrophenyl acetate in water at 25°C are 1.75×10^{-3} and $4 \times 10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ sec}^{-1}$, respectively, demonstrating enhanced reactivity for pyridazine (72JA2765). Neither pyrimidine nor pyrazine was expected to react with the ester sufficiently rapidly to obtain k_2 values.

With the more reactive 2,4-dinitrophenyl acetate, rates were able to be determined for all three diazines (Table VI). A Brønsted plot of this nucleophilic reactivity against $\text{p}K_a$ again showed that while pyrimidine and pyrazine lie close to the line established for pyridine nucleophiles, both pyridazine and its benzo analogue showed considerable rate enhancements. Explanation of this phenomenon involving orbital splitting because of lone-pair repulsions (72CC522; 72JA2765; 73AG(E)36; 73TL2229) is supported by molecular orbital (MO) calculations (71ACR1) and photoelectron spectroscopy (70AG(E)901; 71CRV295). The diazines with more widely spread electron pairs exhibit only minor rate enhancements (72CC522; 72TL189).



SCHEME 9

TABLE VI
SECOND-ORDER RATE COEFFICIENTS^a FOR
HYDROLYSIS OF 2,4-DINITROPHENYL
ACETATE IN WATER^{b,c}

Diazine	pK_a	k_2
Pyridazine	2.44	4.35 ± 0.26
Pyrimidine	1.23	$(2.84 \pm 0.30) \times 10^{-2}$
Pyrazine	(0.65)	$(1.68 \pm 0.08) \times 10^{-2}$
Phthalazine	3.54	50.6 ± 3.4

^a $\text{dm}^3 \text{mol}^{-1} \text{min}^{-1}$.^b At 25°C.^c 72TL189

In contrast to their behavior on alkylation, the amino-, hydroxy-, and thio-substituted azines are subject to almost exclusive exocyclic acylation or aroylation. Acylation or aroylation of the annular nitrogens of pyridazines (47JCS239; 58CPB641; 62CPB936; 62YZ627; 66MI1; 67ACS1067; 73JOC1575), pyrimidines (56JCS2033; 58LA184; 63JCS5590; 64JOC1770; 65JCS7116; 73JCS(P1)1855; 74JCS(P1)1300; 80BAU1662; 81TL1243; 82CHE522), pyrazines (71JCS(C)2977; 73JCS(P1)606; 78CHE227), triazines (70LA177; 72JHC1013; 74AJC1781; 79CB1535), and 3-amino-1,2,4,5-tetrazine (66TL5369) can occur, but they are much less nucleophilic than that of pyridine. Both uracil and thymine may be acylated at N-1 to give products that are powerful acylating agents (58JBC185). Acetylation of 6-amino-1-alkyl- or 6-amino-1,3-dialkyluracils tends to occur at C-5 (81TL1243; 84JHC1129), but if N-1 is unsubstituted, the 6-acetamido derivative is formed, probably via an intramolecular rearrangement of the 1-acetyl intermediate. In N-1-substituted compounds, acylation at C-5 is apparently preferred to unassisted acylation at the exocyclic amino function (72JOC578). There are a number of examples of the preparation of N-acyl and -aroyluracils, -thymines (68JOC1341; 72JHC1423; 83JGU1294; 84TL681), and -barbituric acids (60CPB1021; 68MI1, 68MI2; 79AJC153; 80FES60; 81ZC443; 85AHC229).

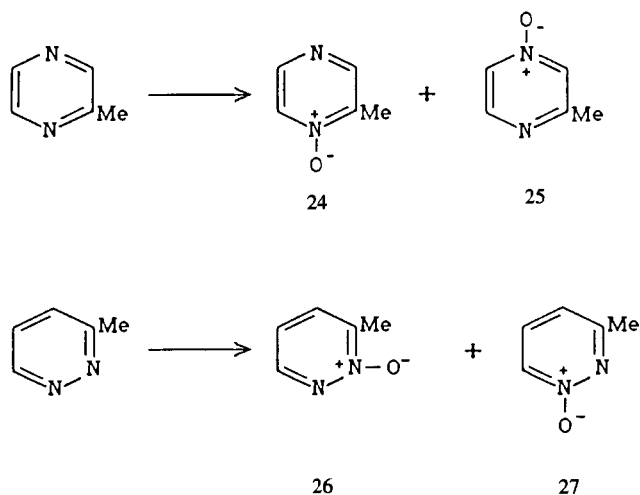
Thus, 1-aminobarbituric acid formed the surprisingly stable 3-benzoyl derivative (79AJC153), while in acetonitrile solution benzoyloxonium salts converted 2,4-*O*-(bistrimethylsilyl) uracil into 40% of the 1-benzoyluracil (83JGU1294). In the presence of triethylamine in DMF (or acetonitrile), 4,6-diaminopyrimidin-2(1*H*)-thione reacted with acid chlorides to give *S*-acyl products in 75–95% yield; a change in the order of addition of the reagents led to different regiochemistry. Thus, when a mixture of the heterocycle and either benzoyl or *p*-toluoyl chloride was added to triethylamine, some 1-aroyl product resulted (80BAU1662). Whereas uracil can be benzoylated at room temperature to give 1-benzoyluracil (**21**) (~90%), excess benzoyl chloride leads to 1,3-dibenzoyluracil (**22**), which can be converted into 3-benzoyluracil (**23**) by mild basic hydrolysis. Decomposition of **22** during chromatography also forms **23**, and it is this behavior that encouraged earlier workers to suggest that routine benzoylation of uracil and thymine gives a mixture of 1- and 3-benzoyl isomers (84TL681). It is likely that the powerful acylating properties of analogous compounds have prevented their isolation and identification on other occasions.

V. N-Oxidation

Although considerable effort has been applied to the synthesis of azine N-oxides, there has been little in the way of quantitative studies. This section updates an earlier review (71MI1), concentrating on information relating to regiochemistry and reactivity.

With the usual oxidants, pyridazine and pyrazine can be oxidized directly, but pyrimidine tends to decompose (67YZ1096) and gives only a very low yield of the N-oxide (84CJC1176). One would not expect diazines and triazines to be oxidized at all readily, and there are many instances in which the reactions fail. Most benzotriazines, for example, are resistant (57JCS3186). The presence, however, of one or more electron-donating groups in the ring increases reactivities many-fold. If the process is similar to the oxidation of pyridines and alkylation of diazines, then it should be second order, with the azine reacting as the free base, and with a ρ value of about -2 . Steric hindrance can, however, be a problem, and unsymmetrical substances give mixtures of mono N-oxides.

The position of oxidation is generally predicted by the use of similar rate factors to those used to predict alkylation positions, but there are exceptions (71JOC787). Nuclear magnetic resonance studies (*vide infra*) have been used to determine product distribution and regiochemistry, and a study of the natural abundance ^{17}O -NMR of azine mono- and di(N-oxides) provides a method of measuring the degree of back-donation from the oxide function (85JHC981). The few applicable kinetic results available for the oxidation of pyridines (60G702; 61G613; 66BSB17) suggest that, as expected, this process may be less susceptible to steric effects than N-methylation. In the azines, 2-methylpyrazine gave a 3:2 ratio of 1- (**24**) and 4-oxides (**25**) (78JOC3367), while methylation gave a 1:4 mixture of 1- and 4-methiodides (71JA5475); 3-methylpyridazine gave a 2.7:1 ratio of 2- (**26**) and 1-oxides (**27**) (63CPB29)



SCHEME 10

compared with the 1:2.6 ratio of methiodides (73ACS383) (Scheme 10). It is difficult to make extensive comparisons since many of the reported isomer ratios are based on low-yield reactions and have not used modern methods of product analysis.

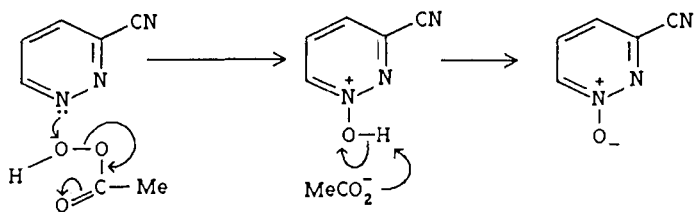
Yields may be low because of steric factors [e.g., 2,6-dimethyl-4-phenylpyrimidine is scarcely oxidized (79CPB2653)], or because there are electron-withdrawing substituents either adjacent to or conjugated with the ring nitrogen [e.g., 2,6-dichloropyrazine gave only 1.2% of the 4-oxide (77JOC1869)], and it is frequently difficult to obtain yields in excess of 50% with many substrates. The presence of N,N-dioxides among the reaction products, particularly with pyrazines, is an added complication in comparison of isomer ratios.

A. PYRIDAZINES

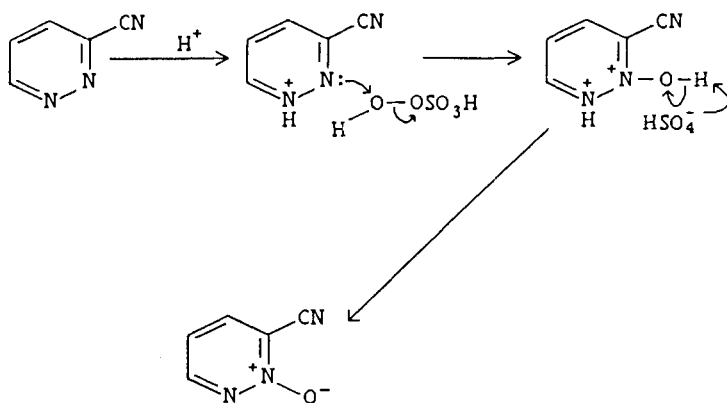
While short-range +I effects assist oxidation of nitrogens closest to methyl groups (63CPB29; 63CPB35; 63CPB721), steric effects still tend to be of greater importance (78H1397). Electron-withdrawing groups retard reaction, and their directional effects favor the more remote annular nitrogen. Thus, 3-chloropyridazine forms the 1-oxide exclusively (60CPB559; 62YZ224), 4-chloro-3,6-dimethylpyridazine gives a 2:1 mixture of 1- and 2-oxides (63CPB337), and there are many other examples involving chloropyridazines (62CPB643; 62CPB989; 62YZ244; 63CPB29; 63CPB35; 63CPB114; 63CPB721). Compounds with more than one halogen are difficult to oxidize, frequently requiring strongly acidic peroxy reagents (62CPB989; 71CC28; 71JCS(C)2867). Peroxysulfuric acid and trifluoroperacetic acid are able to form the N-oxides of such deactivated pyridazines as the 3-cyano and 3-methoxycarbonyl derivatives, but the regiochemistry of oxidation is usually quite different since initial reaction is the protonation of the more basic nitrogen atom. This leads to the preferential formation of 2-oxides (83JHC169) (Scheme 11).

In 3,6-disubstituted pyridazines the competing directive effects of substituents (toward oxidation of the more remote nitrogen) lie in the order $\text{Cl} \approx \text{OR} > \text{Me} > \text{NH}_2$. For example, 3-methoxy-6-methyl- (59CPB938), 3-alkoxy-6-chloro- (62YZ224), 3-alkoxy-6-amino- (63CPB114), and 3-chloro-6-methylpyridazines (63CPB29) all gave mainly the 1-oxides; the 3-amino-6-chloro compound would not react (63CPB114).

3-Amino groups, which are sometimes susceptible to oxidation to nitro (70JOC2478), exert a +M effect on ring nitrogens conjugated with them, leading mainly to 2-oxides (62CPB347; 62CPB936; 63CPB114). Alkoxy groups in the 3-position, though, give 1-oxides (59CPB938; 62YZ584;



Oxidation with peracetic acid



Oxidation with peroxysulfuric acid

SCHEME 11

63AF878) unless in competition with chloro (62YZ584). This must be a direct consequence of steric hindrance by the alkoxy function. Dipole moment measurements show that the groups are in a *cis* orientation, which hinders oxidation at N-2. Even so, it did prove possible to oxidize some 3,6-dialkoxypyridazines, but not the di-*t*-butoxy and dibenzyloxy derivatives (55YZ966; 66YZ314).

Groups in the 4-position influence the direction of N-oxidation largely through their inductive effects. 4-Chloro-3,6-dimethylpyridazine gave a 2:1 ratio of the isomeric 1- and 2-oxides (63CPB337), but the low yield (17%) of 1- and 2-oxides (2.5:1) isolated from 3,6-dichloro-4-methoxypyridazine (62CPB643) may imply some +M effect of methoxy.

Pyridazine 1,2-dioxides can be prepared in poor yield under forcing condition (68TL1855; 70CPB1211).

B. PYRIMIDINES

Generally pyrimidines and methylpyrimidines are more susceptible to side reactions (decomposition, ring-carbon oxidation, ring-opening) accompanying N-oxidation than other π -deficient diazines and triazines, and successful direct N-oxidation of pyrimidines usually needs activating substituents to be present (78AJC2517; 81H573; 84CJC1176). If strong acid is present in the oxidizing medium, no N-oxides are formed; instead, low yields of pyrimidinones appear (85JOC3073).

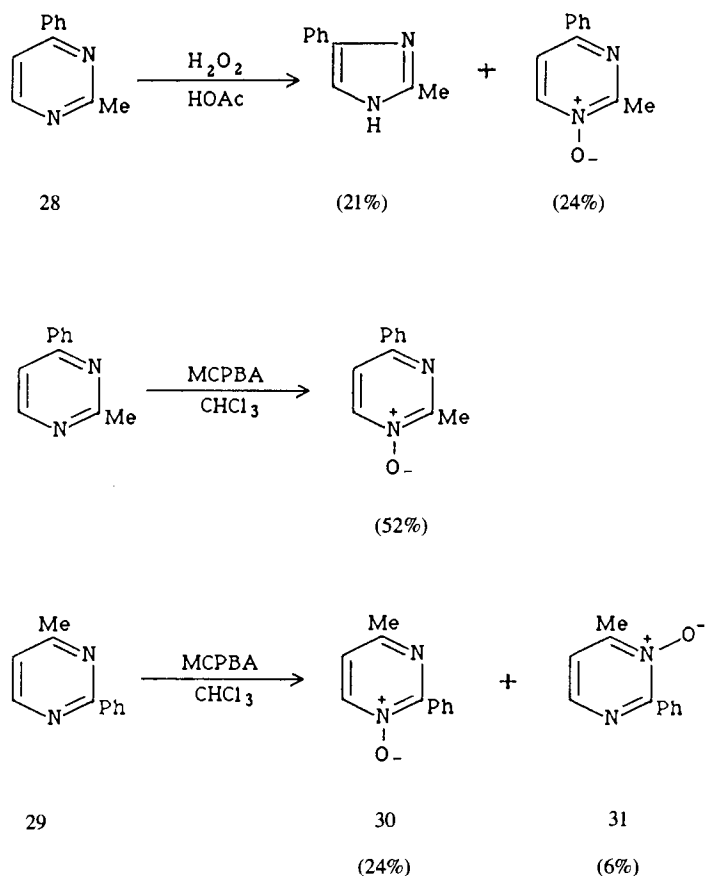
When the 6-position is unsubstituted, oxidative degradation is most common, and peracetic acid treatment leads to ring contraction to form 2,4-disubstituted imidazoles and their N-oxides (81H573). For example, 2-methyl-4-phenylpyrimidine (**28**) reacts in this way with peracetic acid, but with *m*-chloroperbenzoic acid in chloroform, pyrimidine N-oxides were formed as well (Scheme 12). Even pyrimidine itself gave the oxide in 48% yield under these latter conditions; 2-methylpyrimidine gave 55% of the N-oxide (81H573).

Unless the ring is very highly activated, pyrimidine 1,3-dioxides are seldom directly accessible (68JHC449; 80AJC131; 83CHE1003).

Factors affecting the orientation of N-oxidation can be summarized as follows: Bulky groups and electron-withdrawing substituents decrease the facility of oxidation and direct attack to the more remote nitrogen; unsymmetrical pyrimidines are oxidized preferentially at sites *para* to strong electron donors; weaker +I groups are more likely to be *ortho* directors (69JOC2153; 78AJC2517; 84CJC1176). As mentioned above, careful choice of reagent is necessary to avoid preferential oxidative degradation (81H573). The use of ^1H NMR assisted by lanthanide shift reagents has proved valuable in distinction of the 1- and 3-oxides (77H257), but ^{15}N NMR was unreliable for determining the oxidation site in pyrimidine-2,4-diamine (81AJC1539).

Steric hindrance to attack is common with the phenyl substituent (79CPB2653; 81H573; 83CHE1003; 84CJC1176). Using *m*-chloroperbenzoic (MCPBA) acid in chloroform (conditions which reduce ring decomposition, *vide supra*), 2-phenylpyrimidine gave only a 13% yield of the oxide (cf. 2-methylpyrimidine, which gave 55%); 4-phenyl- (64%), 2-methyl-4-phenyl- (52%), and 2,4-diphenylpyrimidine (15%) all gave only the 1-oxide. In unsymmetrical pyrimidines with the aryl group in the 2-position, both 1- and 3-oxides can be formed with steric effects again exerting the major influence. Thus, from 4-methyl-2-phenylpyrimidine (**29**) a 4:1 mixture of the 1- (**30**) and 3- (**31**) oxides was detected (81H573) (Scheme 12).

The steric effects of simple alkyl groups are smaller. 4-Methylpyrimidine has been variously reported as giving a 1:1 (84CJC1176), 1:2.5 (81H573), or



SCHEME 12

1:3 (64TL19) ratio of the 1- and 3-oxides, depending on the reagent. 2,4-Dimethylpyrimidine gave a 1:1 mixture (81H573; 83CPB4533), while the 4,6-dimethyl isomer gave a 75% yield of the only possible monoxide (84CJC1176). Larger alkyl groups have a much greater influence on the 1-:3-isomer ratios, for example 4-ethyl-3,6-dimethyl- (6:5), 4-ethyl-2-isopropyl-6-methyl- (3:2), 4-ethyl-6-methyl-2-phenyl- (2:1), and 4-benzyl-2,6-dimethyl-pyrimidine (1:1) (79CPB2653), while 4-methyl-2-phenylpyrimidine gave a 9% yield of 1-oxide and a trace of the 3-isomer (81H573).

Nitro groups may inhibit reaction completely, as with the 5-nitro (68JHC449) and 2,4-diamino-6-methyl-5-nitro (79AJC2049) compounds, or allow some reaction if sufficient alternative activation is present. The 3-oxide

is formed from oxidation of 2,4-diamino-6-methylamino-5-nitropyrimidine (79AJC2049). With hydrogen peroxide in trifluoroacetic acid, 4,6-diamino-5-nitrosopyrimidine is converted into a mixture of the 4,6-diamino-5-nitropyrimidine, 4,6-diamino-2-hydroxy-5-nitropyrimidine, and a small quantity of 4,6-diamino-5-nitropyrimidine 1,3-dioxide (68JHC449; 80AJC131). The method is not general for the direct synthesis of pyrimidine 1,3-dioxides, which are, however, available indirectly from the manganese dioxide oxidation of 1-hydroxy-1,2,5,6-tetrahydropyrimidine 1-oxides (75TL2721). 2-Chloro groups also prevent reaction (84CJC1176), although the 4-chloro-6-methyl compound gave a small amount of 1-oxide (74RTC58), and 5-bromopyrimidine was oxidized by *m*-chloroperbenzoic acid to give a 29% yield of the 1-oxide (85JOC3073).

Both 4-methoxy- and 4-methoxy-6-methylpyrimidines gave only 1-oxides in 29 and 70% yields when treated with peracetic acid (84CJC1176). With *m*-chloroperbenzoic acid, the former gave 44% of the 1-oxide only; 4-methoxy-2-methyl- and 4-methoxy-2-phenylpyrimidines also gave 1-oxides exclusively in 60 and 32% yields, respectively (81H573). The more hindered 4-methoxy-2-methoxymethyl-6-methylpyrimidine and its 6-methoxymethyl-2-methyl isomer reacted with the same regiochemistry (84CPB728). 2-Methoxypyrimidine gave a low (18%) yield of N-oxide with peracetic acid (84CJC1176), but with *m*-chloroperbenzoic acid, 2-methoxy-, 2-methoxy-4-methyl-, and 2,4-dimethoxypyrimidines failed to form oxides (81H573). These results point to steric hindrance by methoxyl as the major factor, with perhaps some +M effect on the *p*-nitrogen, since 4-methoxypyrimidine was readily converted by *m*-chloroperbenzoic acid into 70% (85JOC3073) or 44% (81H573) of the 1-oxide. The 4-methoxy-2-methyl and 4-methoxy-2-phenyl derivatives also gave 1-oxides (81H573), as did 5-bromo-4-ethoxypyrimidine, when treated with trifluoroperacetic acid (79CPB2291).

The behavior of amino groups in the 4-position provides the best evidence for the operation of +M effects in the series. With peracetic acid, 4-amino-, 4-methylamino, and 4-dimethylaminopyrimidines gave low yields (25, 11, and 10%, respectively) of the 1-oxides (a trace of 3-oxide was also detected in reaction of the amino derivative) (79CPB2653; 84CJC1176). 6-Methyl-4-aminopyrimidine (36%) and its 4-methylamino analogue (33%) followed the same trend. This behavior of 4-amino groups parallels observed *ortho*-directing effects in the 3-aminopyridazines and aminotriazines. In 2-aminopyrimidines, however, oxidation does occur at an *ortho* nitrogen for amino (40%), methylamino (30%), but not dimethylamino or acetamido groups (84CJC1176). 2,4-Diaminopyrimidines oxidize normally at N-3 (81AJC1539; 84AJC1195), but 2,4,6-triaminopyrimidines with amino, alkyl, aryl, halogen, or thiol groups at the 5-position usually fail to give N-oxides. Instead, they frequently form aminotriazines through attack of the oxidizing agent at C-5

(70JHC1183; 73CB3194; 84CPB728). Exceptions seem to be 2,4-diamino-5-ethynyl- and 2,4-diamino-6-chloro-5-ethylpyrimidines, which give 3-oxides (84AJC1195).

The short-range +I effects of methyl groups are evident from the isolation of 46 and 38% yields of 3-oxides from 2-amino-4-methyl- and 2-methylamino-4-methylpyrimidines. In the former reaction, 7% of the 1-oxide was also observed (84CJC1176).

Uracil and thymine did not form N-oxides when treated with *m*-chloroperbenzoic acid (86CPB2354). Indeed, the only reported N-oxidation of a tautomerizable hydroxypyrimidine refers to 2,6-diamino-5,5-diethylpyrimidin-4(5*H*)-one, which reacted with trifluoroperacetic acid at the N-1 position (78AJC2517). In 5-hydroxypyrimidines, though, the hydroxy function is phenolic and assists N-oxidation to the extent that steric effects of adjacent alkyl groups are largely overcome. For example, with *p*-nitroperbenzoic acid, 5-hydroxy-2-isopropyl-4,6-dimethylpyrimidine gave the 1-oxide in 82% yield (83CHE1003); 5-hydroxy-4-phenylpyrimidine reacted less readily to give 37% of the 1-oxide (83CHE1008).

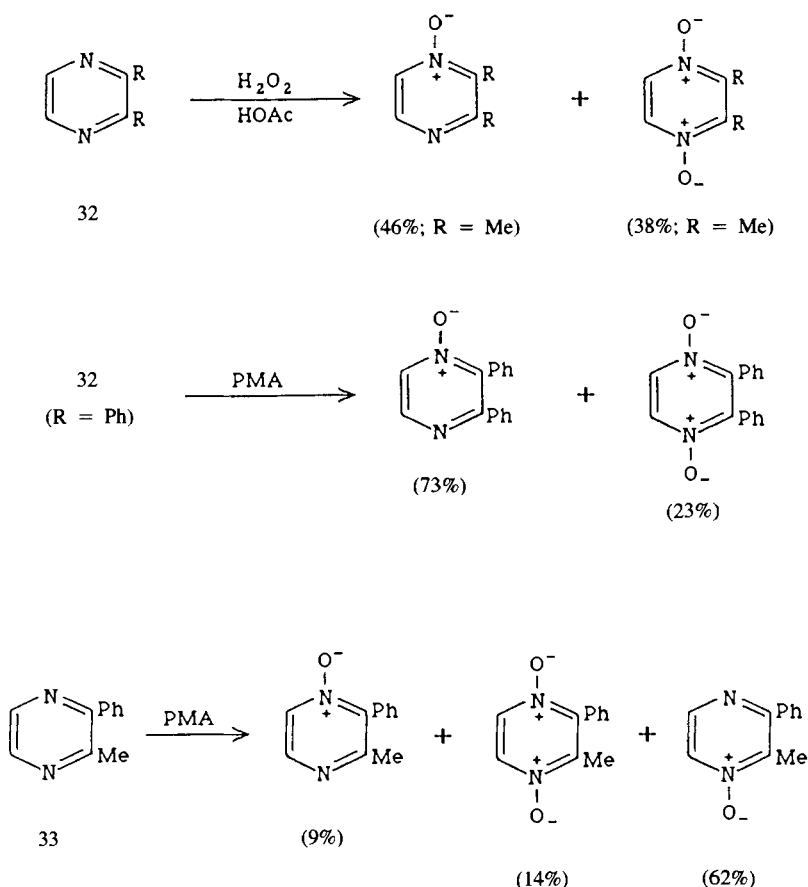
C. PYRAZINES

Depending on reagent, temperature, and reaction time, pyrazines can be transformed into mono- or dioxides, with di(N-oxidation) apparently much easier than with the other diazines. Thus, 2-hydroxypyrazine 1,4-dioxides have been prepared in 18–42% yield by treatment of the pyrazines with permaleic acid (81JHC555). While the electronic natures of the substituents have a bearing on the sites and rates of oxidation, steric effects again frequently play a decisive role. Thus, many 2-substituted pyrazines form mainly 4-oxides with the usual range of peroxy reagents. For example, 2-propylpyrazine gave a 5:7 ratio of 1- and 4-oxides (82JHC1061), both the 2-isobutyl-5-isopropyl- (78CPB2046) and 2-methyl-3-phenylpyrazines (82JHC465) gave a 7:1 ratio, 2-phenylpyrazine formed only the 4-oxide (78JOC3367; 81JHC555; 82JHC1061) as did the 2,6-diphenyl (56JCS1885; 83JHC311) and 2-methyl-6-phenyl compounds (83JHC311). Lower yields from the phenylpyrazines are probably a function of electron withdrawal by the substituent.

Only methyl groups seem to cause little steric hindrance, and hence 2-methylpyrazine was converted by peracetic acid into a 3:2 mixture of 1- and 4-oxides (78JOC3367), the preponderance of the former arising from the +I, +M effects of methyl. The 2,6-dimethyl compound has been variously reported to form a 1:1 mixture of monoxides, with a small amount of dioxide (59JA5160), or a 1:2 mixture of 1- and 4-oxides (83JHC311). Both the 2,3- (82JHC465) (32; R = Me) and 2,5-dimethyl isomers (58JOC1603), and

tetramethylpyrazine (59JA5160) formed mono- and dioxides readily under similar conditions, as did the more hindered 2,3-diphenyl derivative (56JCS1885; 82JHC465) (**32**; R = Ph). 2-Methyl-3-phenylpyrazine (**33**) reacted with permaleic acid (PMA) to give a mixture of products which reflects the steric and electronic effects of substituents (82JHC465) (Scheme 13). Symmetrical 2,3-di-(*p*-substituted) phenylpyrazines gave 60–75% monoxide and 5–15% dioxide under similar conditions (84JHC103).

Alkoxy groups again direct attack to the more remote nitrogen site, probably for steric reasons. Thus, 2-ethoxypyrazine gave 45% and 2-methoxy-3-methylpyrazine 82% of the 4-oxides (64JOC2623). Isolation of an almost quantitative yield of 4-oxide from 2-methoxy-3-phenylpyrazine oxidation



SCHEME 13

(56JA4071) may be a consequence of the aryl group being twisted out of conjugation by the adjacent ether function.

Electron-donating amino substituents activate the adjacent ring nitrogen to oxidation by *m*-chloroperbenzoic acid, but added methyl and phenyl groups may modify this orientating effect (85JHC1145). While 2-aminopyrazine gave a 63% yield of the 1-oxide, 2-amino-3-methylpyrazine gave a 19:1 mixture of the 1- and 3-oxides; with the 2-amino-5-methyl isomer, the ratio was 17:3, but with 2-amino-3- and 2-amino-5-phenylpyrazines only the 1-oxides were formed (85JHC1145).

Strongly electron-withdrawing chloro groups deactivate the ring, particularly at adjacent nitrogens, and 4-oxides usually result (63JOC1682; 64JOC1645; 70JCS(C)1070; 77JOC1869; 78JOC3367; 81CPB88; 82JHC465; 83JHC311) even if there are bulky groups such as isobutyl (78CPB2046; 80CPB2734), *sec*-butyl (85JHC1291), or phenyl (78JOC3367; 82JHC465) at the 3-position. Increased steric hindrance to 4-oxidation is indicated by the observations that equal proportions of both possible oxides are formed from 2-chloro-5-phenylpyrazine (78JOC3367) [a variety of *para* substituents in the phenyl ring modifies this 1:1 ratio to some extent (80CPB2734)], that only 4-oxide (96%) results from 3-chloro-2,6-diphenylpyrazine oxidation, and that mixtures of oxides are obtained from 3-chloro-2-methyl-6-phenyl- and 5-chloro-2-methyl-6-phenylpyrazines. In the first of these last two compounds, the yields of 1-, 4-, and 1,4-dioxides were 18, 22, and 3%; comparative results for the second were 28, 17, and 21% (83JHC311). There have been suggestions that conjugative effects of phenyl substituents are involved in determination of product regiochemistry, however, the evidence is not compelling (78JOC3367) [but see (80CPB2734)]. The methyl ester of 6-chloro-2-pyrazinoic acid gave only the 1-oxide with *m*-chloroperbenzoic acid (81CPB88). When more than one chlorine atom is present, N-oxidation may be inhibited completely (77JOC1869), or merely retarded. Some 2,6-dichloropyrazines formed low yields of 4-oxides (77JOC1869; 83JHC311). A 1:1 ratio of 1- and 4-oxides was obtained from 2-acetamidopyrazine (68KGS725). 2-Hydroxy-3,6-di(*sec*-butyl)pyrazine is converted into the 4-oxide (85%) by permaleic acid (85JHC1291).

If a strongly acidic peracid is used, the orientation of oxidation usually changes, since the initial reaction is protonation of the more basic ring nitrogen. Both 2-methyl- and 2-phenylpyrazines are sufficiently strong bases to be diprotonated by Caro's acid, and they resist N-oxidation (Table VII). However, chloropyrazines are only monoprotonated at the nitrogen remote from the chlorine atom, ensuring that oxidation occurs (with some difficulty) at the nitrogen adjacent to the halogen. Similar considerations apply to 2-cyano- and 2-methoxycarbonylpyrazines (71CC28; 71JHC697; 77JOC1869; 78JOC3367; 81JHC555; 83JHC169), although 2-pyrazinoic acid and its amide

TABLE VII
N-OXIDATION OF PYRAZINES WITH PERACETIC AND
PEROXYSLFURIC ACIDS^a

Substituent	Orientation of oxidation (yield)	
	Peracetic acid	Peroxyulfuric acid
2-Me	1-, 4- (3:2; 64%)	(0%)
2-Ph	4- (28%)	4- (2.5%)
2-Cl	4- (61%)	1- (22%)
2-Cl-3-Ph	4- (51%)	1- (21%)
2-Cl-6-Ph	4- (89%)	(0%)
2-Cl-5-Ph	1-, 4- (1:1; 33%)	1- (26%)

^a 78JOC3367; 81JHC555.

were not oxidized by H₂SO₅ (83JHC169). Sodium perborate has been recommended as a less hazardous reagent than excess peracetic acid for water-soluble pyrazines (85S216).

D. TRIAZINES

With peracids, substituted 1,2,3-triazines [the parent compound gave only a trace of 2-oxide (86CPB109)] can give rise to 1-, 3-, or 2-oxides, the latter usually predominating even for symmetrical compounds in spite of the statistical effect. Total yields are between 40 and 90%. As with other azines, there is a significant proportion of oxidation on a nitrogen next to a methyl group as a result of its +I, +M effects, but yields are generally quite low at these sites (15–29%), suggesting that the electron-donating effects are not large. Even in the less hindered 2-position, methyltriazines gave only moderate yields (17–48%) of N-oxide. 4-Methyl-1,2,3-triazine gave a 1:3 (80CC1182) or 1:2 (86CPB109) ratio of the 3- and 2-oxides (no 1-oxide was detected); the 4,6-dimethyltriazine (1:2.4) (80CC1182; 86H33), and 4,5,6-trimethyltriazine [1:2 (86CPB109) or 1:3 (80CC1182)] both gave more of the 2- than the 1-oxides. The more hindered 4-methyl-6-phenyl derivative formed twice as much 2-oxide as 3-oxide. Again no 1-oxidation was observed with this substrate (80CC1182; 86CPB109). The observation that 1-oxides are not detected when C-6 (adjacent to the target nitrogen atom) is unsubstituted is difficult to explain. Perhaps the 1-oxides are formed, but decompose under the oxidizing conditions (86CPB109). Although in earlier references (78HC3; 85LA1732) it was reported that 4,5,6-triphenyl-1,2,3-triazine formed a 1-oxide, a crystal structure determination (86CPB109) has shown the peracetic acid product

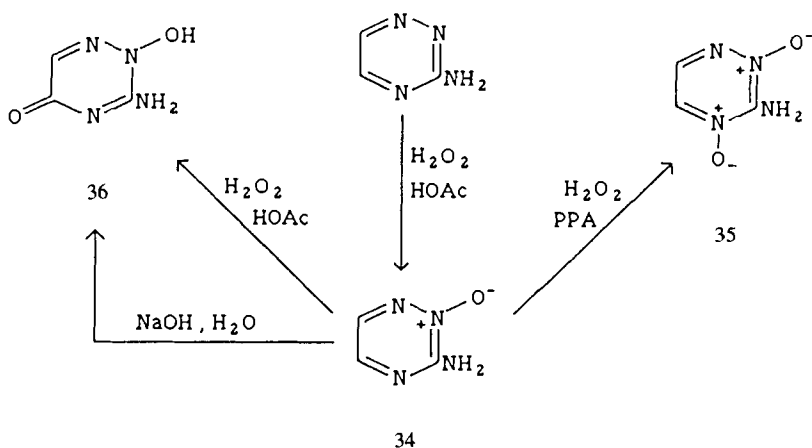
to be the expected 2-oxide, which also forms in 53% yield when *m*-chloroperbenzoic acid is used as oxidant. Both 4-phenyl- and 4,6-diphenyl-triazines were only oxidized at N-2, as was 5-methyl-1,2,3-triazine in 17% yield (86CPB109). That no products were observed with an N-oxide function adjacent to a phenyl group can probably be explained by steric factors (86CPB109).

In 1,2,4-triazines it is essential that the 5-position is blocked (cf. pyrimidines without 4- or 6-substituents) to prevent nucleophilic ring opening, oxidation, and ring contractions from competing with N-oxidation (72LA111; 86H951). Products include 1,2,4-triazin-5-ones and -5,6-diones (72LA111). Whereas 1,2,4-triazin-3-ones were oxidized by peracid to the 3,5-diones, (69JHC403), 5-substituted analogues gave 1-oxides under the same reaction conditions (66JOC3914).

5-Alkyl and 5-aryl substituents direct attack of peracids to the 1-position. Thus, the 5-methyl, 5-phenyl, 5,6-dimethyl, and 3,5- and 5,6-diphenyl compounds all gave the 1-oxides (71JOC787; 78CB240), as did a series of 3-aryl-1,2,4-triazines substituted at the 5,6-positions by alicyclic rings (82JHC1201). One might have expected the products to be 2- or 4-oxides by analogy with other diazines, but 4-oxides are only accessible by ring-synthetic methods (71LA12; 78CB240). The 3,5,6-triphenyl-1,2,4-triazine formed a 4:1 ratio of 1- and 2-oxides (64JCS4209).

In common with other azines, methoxy or phenoxy groups direct attack to the more remote nitrogen atom; 3-methoxy-1,2,4-triazines give 1-oxides (71JOC787; 78RTC273). Only with 3-amino- and 3-alkylamino-1,2,4-triazines are the 2-oxides formed (71JOC787; 77JOC546; 85H1969). In contrast, 3-dimethylamino-1,2,4-triazine forms the 1-oxide, perhaps because of steric hindrance. The 2-oxides of dialkylamino-1,2,4-triazines are, however, readily accessible when secondary amines react with 3-bromo-1,2,4-triazine 2-oxide. An alternative explanation for the seemingly anomalous N-oxidation behavior of 3-dimethylamino-1,2,4-triazine is the possibility that 3-amino-3-imino tautomerism may be necessary for 2-oxidation to occur (77JOC546). Earlier reports had designated the 3-amino 2-oxides as 1-oxides (64CPB1329; 65CPB1168; 66JOC3914; 66JOC3917), but examination of ¹H-, ¹³C-, and ¹⁵N-NMR shifts has been valuable in determining the true oxidation position(s) (71JOC787; 75CJC3419; 77JOC546; 82JHC1201; 85H1969; 86H951). With 3-amino-5-phenyl-1,2,4-triazine, the major product is the 2-oxide, but some 1-oxide is formed as well (71JOC787).

Peracetic acid oxidizes 3-phenyl-5,6-dimethyl-1,2,4-triazine 4-oxide to the 1,4-dioxide (78HC3), but under the same conditions 3,6-diphenyl-1,2,4-triazine 4-oxide (no 5-substituent) gave 3,6-diphenyl-1,2,4-triazin-5(2*H*)-one, which on further oxidation gave its 1,4-dioxide (78HC3). The first example has been reported of a 1,2,4-triazine di(N-oxide) prepared from a triazine with no



SCHEME 14

5-substituent (86H951). With hydrogen peroxide in polyphosphoric acid (a medium in which covalent hydration at C-5 may be suppressed), 3-amino-1,2,4-triazine 2-oxide (34) was converted into the 2,4-dioxide (35). Oxidation with peracetic or trifluoroperacetic acids gave 3-amino-2-hydroxy-1,2,4-triazin-5(2H)-one (36), which is also formed on hydrolysis of the same substrate with warm NaOH (86H951) (Scheme 14).

2,4-Diamino-6-chloromethyl-1,3,5-triazine formed the 3-oxide (67JHC268). There has yet been no reported N-oxidation of a tetrazine.

VI. N-Amination

Few examples of N-amination of azines have been reported. The use of such reagents as *O*-mesitylenesulfonylhydroxylamine has led to the direct synthesis of *N*-aminopyridazinium, -pyrimidinium, and -pyrazinium salts (80CPB2676), and 1-aminobarbituric acids (72CPB1814), while *O*-(2,4-dinitrophenyl)hydroxylamine was a useful amino-transfer reagent in the direct synthesis of 1-amino-6-methylthio-1,2,4-triazin-4(1H)-ones from 2-methylthio-1,2,4-triazin-5(1H)-ones (82JHC1583).

The N-amination of 3-aminopyridazines occurs next to the amino function (75JHC107; 81T1787), while 3-methylpyridazine and its 6-methoxy derivative followed the trend of N-alkylation being aminated at N-2 (72CPB1814). 3-Methoxypyridazine gave the 1-amino salt as expected (71CPB2106).

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The Quantitative Analysis of Steric Effects in Heteroaromatics

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I. Introduction

Understanding, rationalizing, and predicting both reactivity and the energetics of dynamic stereochemistry are of major importance in heterocyclic chemistry and one or both of these topics are a concern of the majority of the contributions in *Advances in Heterocyclic Chemistry*. No previous systematic study has been reported which treats quantitatively steric effects in heteroaromatics; this is the purpose of this article.

The reason for writing this article is that important progress in the quantitative analysis of steric effects in heteroaromatics has been made recently by linear free energy relationships (LFER), geometrical, and theoretical methods. Also, heterocycles have been used to propose and exemplify new concepts and new parameters in physical organic chemistry.

Our article will be mostly concerned with the importance of steric effects in rationalizing the reactivity and dynamic stereochemistry of heteroaromatics and with recent attempts to bridge the gap between them; these topics correspond to three major sections of the chapter.

The heteroaromatic molecules considered are essentially those having a 6π -electron system, as described in the recent *Handbook of Heterocyclic Chemistry* (85MI1): They are formally derived from benzene by replacement of one annular CH group by a trivalent or two adjacent CH groups by a divalent heteroatom. Thus, the replacement of one CH group in benzene by O^+ , S^+ , or N gives the six-membered pyrylium, thiinium, or pyridine, while replacement of two adjacent CH groups in benzene by O, S, or NH gives the five-membered furan, thiophene, or pyrrole. This produces a classification into a six- or five-membered ring which, in fact, is not arbitrary when studying steric effects,

because reactions "in the plane of the ring" (like quaternization), reactions "out of the plane" (like nucleophilic or electrophilic heteroaromatic substitutions), and barriers to rotation are strongly dependent upon the size of the ring and on associated steric strain. Related to these heteroaromatics are their benzo analogues, obtained by successive addition of one or two benzo-fused rings (e.g., pyridine giving quinoline and acridine among other fused heterocycles). Also multiple replacement of one or two annular CH groups by two or several heteroatoms will be considered (e.g., replacement of two CH groups in benzene by two N atoms in 1,2-, 1,3-, and 1,4-positions giving pyridazine, pyrimidine, and pyrazine).

The number of publications in which steric effects are reported is such that a complete coverage of all would be too lengthy; we have rather selected articles in which steric effects are studied quantitatively.

II. Rates and Equilibria: Intermolecular Steric Effects

In this section, we concentrate on the influence of steric effects on heterocyclic reactivity, but we do not treat reactions of substituents bonded to heteroaromatics, except in special cases of ambident reactivity (ring vs. substituent) modified by steric effects.

A. SEPARATION OF STERIC AND ELECTRONIC EFFECTS

A major difficulty in studying steric effects is the separation of steric from inductive and resonance effects. It is clearly impossible to encounter the steric effect of a substituent without having at the same time the electronic effect of the same substituent. Indeed, although early works on the qualitative influence of steric effects on chemical reactions were reported by the end of the last century by Hofmann (1872CB704), Kehrmann (1888CB3315), and Meyer (1894CB1580), no systematic work was begun in heterocyclic chemistry until 1950, when H. C. Brown started to study steric effects in amines and more specifically in heteroaromatics. For instance, steric effects are not treated in the pioneering work of Hammett, who proposed a most useful tool in structure:(re)activity studies with the LFER (40MI1). It is easy to find positions on an aromatic or heteroaromatic molecule where steric effects are absent (meta or para to a reactive center), whereas in an ortho position there will always be both a steric and an electronic effect. Different methods may be appropriate whether qualitative or quantitative results are expected.

One of the simplest methods to evaluate the steric effect of a substituent, in a position ortho to a reactive center, is to compare results for the same group at a

para position. In the absence of steric and hydrogen bonding factors, the electronic effects of ortho groups should be proportional to those of para substituents. This oversimplification is useful in predicting regioselectivity in electrophilic aromatic substitution reactions (53CRV191), but it was shown to be incorrect in heteroaromatics by Charton, who concluded from a statistical analysis that ortho positions in heteroaromatics are better described by σ_m rather than by σ_p parameters (64JA2033).

A very useful and rather precise method consists of studying series with substituents having (almost) the same electronic effect and very different steric requirements. Alkyl groups are a typical example, and more precisely the α -series proposed by Ingold (methyl, ethyl, isopropyl, *t*-butyl) (57QR1); this is the series widely investigated by H. C. Brown (56JCS1248; 59JCE424). In some cases, the series is limited to methyl and *t*-butyl, which behave as monitors of steric effects (76T2451; 78AG(E)593; 78T1). A better understanding of the conformational dependence of steric effects needs other alkyl groups, such as those of the β -series (ethyl, *n*-propyl, isobutyl, neopentyl) (67BSF4502; 78AP650; 79BSF(2)484). Note that the methyl group is the reference in all these cases (not H as in the Hammett and derived equations), because all theoretical and experimental models indicate a large difference in electronic effects between hydrogen and methyl and a very small one between methyl and all other alkyl groups.

When incorporating substituents other than alkyl or when introducing a large set of substituents, including functional groups with large electron-donating or -withdrawing effect, a more appropriate method is needed. This can be done by estimating electronic effects of ortho substituents from pK_a values or from σ parameters.

For heteroaromatics having a basicity which can be measured precisely by conventional potentiometric or spectrophotometric methods, a pK_a value is easily obtained. Owing to the very small size of the proton, the pK_a is considered free from steric effects. Thus, the nucleophilicity of a series of heteroaromatic molecules, say in quaternization reactions, may be compared to the pK_a within the same series; this is a Brönsted relation:

$$\log(k/k_H) = \alpha pK_a$$

where k_H refers to the unsubstituted molecule (and H is the reference substituent). Downward deviations from this equation provide a measure of the steric effect of the substituent in the given reaction. We believe that deviations from the Brönsted equation are very useful in the quantitative estimation of steric effects, and we wish to address negative remarks which are sometimes made concerning the analytical use of the Brönsted equation.

Remark a. Since nucleophilicity corresponds to rate constants and is kinetically controlled and basicity corresponds to equilibria and is thermody-

namically controlled, they are not strictly comparable. Answer: This is exactly the problem of the Hammett and Taft equations and of LFER in general.

Remark b. Because nucleophilicity is usually recorded in organic solvents and pK_a in water (or water/methanol mixtures), this can make a large difference. Answer: The nucleophilicities of a series of molecules in different organic solvents are correlated with excellent correlation coefficients (r). Furthermore, correlations of each series with pK_a in the case of non-ortho substituents is also very good. That the slope, α , of the Brönsted relation is an estimate of transition state location may be questioned (78T2331). Deviations from the Brönsted α seem to be well established as a measure of steric effects.

Remark c. Values for pK_a are not strictly independent of steric effects. Answer: This idea originated in the study of steric effects on solution-phase basicities of 2-alkyl- and 2,6-dialkylpyridines by H. C. Brown (53JA3865; 55JA1727; 66JA986). From this work, it was concluded that the influence of an alkyl group on the base strength is in general additive. This is illustrated by the experimental and calculated pK_a of polymethylpyridines, including 2,6-derivatives (Table I) and by the effect of alkyl groups in the 2,6-positions on the strength of pyridine bases (Fig. 1). Additivity fails completely in the series pyridine ($pK_a = 4.38$), 2-*t*-butylpyridine ($pK_a = 4.68$), and 2,6-di-*t*-butylpyridine ($pK_a = 3.58$).

The fact that the pK_a of the 2,6-di-*t*-butylpyridine (2,6-DTBP) is about 1.4 units lower than expected was ascribed to the steric requirements of the bulky *t*-butyl groups. Three possible explanations were postulated: (1) the N—H bond in protonated 2,6-DTBP (2,6-DTBPH⁺) is directly compressed by the *t*-butyl groups; (2) hydrogen bonding of 2,6-DTBPH⁺ with the solvent is strongly reduced; and (3) the overall electrostatic solvation of 2,6-DTBPH⁺ is prevented by steric hindrance. Further studies by Mc Daniel and Oczan favored steric inhibition of solvation of 2,6-DTBPH⁺ (68JOC1922); this was also the conclusion of Condon from independent studies (65JA4494). Taft

TABLE I
 pK_a OF POLYMETHYLPYRIDINES IN WATER

Methylpyridine	$pK_a(\text{obs})$	δpK_a	$pK_a(\text{calc})$	$pK_a(\text{obs} - \text{calc})$
H	5.19	0		
2	5.96	0.97		
3	5.68	0.49		
4	6.02	0.83		
2,6	6.72		6.73	0.01
2,4,6	7.63		7.56	0.07
2,3,4,6	8.10		8.05	-0.05

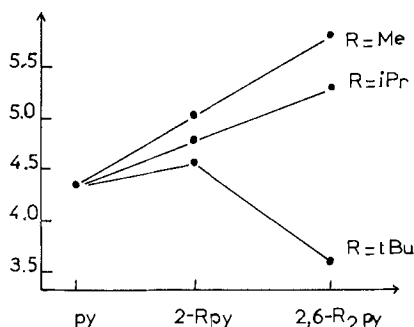


FIG. 1. Effect of alkyl groups in the 2,6-positions on the strength of pyridine bases (in 50% ethanol).

et al. (75JA2904) and Aue *et al.* (76JA854) ruled out the possibility of direct compression of the NH^+ because the gas-phase basicity of 2,6-DTBP is close to that predicted from additivity of other *t*-butylpyridines (TBP). Evidence favored a reduced solvent effect whose nature had to be specified. Arnett and Chawla (79JA7141) concluded from measured and estimated data of protonation in the gas and aqueous phases that steric hindrance totally precludes hydrogen bonding of a water molecule to both the cation and neutral species. Le Noble and Asano (75JOC1179) and Hopkins and Ali (77JA2069) reported entropy and volume changes for the protonation of 2,6-DTBP in solution. These results cannot be ascribed to hydrogen bonding or steric hindrance to solvation. The large entropy changes found in DTBP protonation are not due to an absence of solvation. A possible explanation was hindered rotations on protonation of 2,6-DTBP evidence by ^{13}C NMR (80JPC203; 80JPC2814).

A study by Aue and co-workers (84JA4341) gave a picture consistent with all the data: "(a) the aqueous 2,6-DTBPH⁺ is hydrogen bonded to a water molecule via a NH bond; (b) in the aqueous solvation complex of the 2,6-DTBPH⁺ cation several internal rotations are substantially restricted because steric interactions cause a loss of entropy; (c) in pure water a significant fraction of aqueous 2,6-DTBP is also hydrogen bonded to a water molecule at the pyridine nitrogen." This is a satisfactory explanation to a difficult problem that occurs only with *o,o'*-di-*t*-butylpyridines and -pyrimidines (78RTC159) or with *ortho,ortho'*-disubstituted pyridines with large groups like benzo or phenyl (84CSR47; 85H1765). Steric effects interfere significantly with pK_a only with very bulky 2,6-DTBP or related analogues. Since these molecules are basic and not nucleophilic amines (see in Section V selected examples of their use), the Brönsted relation is unlikely to be applied to these heteroaromatic amines whose nucleophilic reactivity is so reduced that it can hardly operate even under high pressure (63MI1; 70T4119; 75JA1778; 75JA4015; 85JCS(F1)2437). In other words, steric effects

modify significantly the pK_a values only of overcrowded heteroaromatics and will give no Brönsted relation. In one example, however, the ΔpK_a values (measured – calculated) of overcrowded pyridines are correlated with dequaternization rates of the corresponding pyridinium ions. In fact, in this case the pyridinium ions are not made by quaternization of pyridines but from reaction of amines with pyrylium ions (83JCS(P2)45).

Evaluation of steric effects can also be made by separating electronic from steric effects with the help of linear free energy relationship and appropriate parameters. Applications of the Hammett equation to heterocycles have been reviewed (64AHC(3)209; 76AHC(20)1) and the influence of substituent effects on the basicity and N-alkylation of pyridines, which have been by far the most widely studied, shows the difficulties in this approach. Jaffe and Jones (64AHC(3)209) reported a good correlation between pK_a of 3- and 4-substituted pyridines and Hammett σ parameters (σ_p in position-4, σ_m in position-3). The equation

$$\log(k/k_H) = \rho\sigma$$

has been used (81JCS(P2)409) to correlate rate constants for the reaction between 3- and 4-substituted pyridines and ethyl iodide in various solvents. A problem arises when incorporating ortho substituents to treat steric effects, because no σ ortho parameter exists. A possibility, following the analysis by Charton (64JA2033), is to use σ_m parameters, which surprisingly were found to describe ortho positions in heterocycles better than σ_p . This was experimentally verified by Forlani *et al.* (79JCS(P2)163), who obtained good correlations between 2-substituted thiazoles and σ_m and by Seydel *et al.* who correlated a large series of 2-R-pyridine pK_a values with σ_i (76JMC483). However, the approach of using a single σ parameter has been criticized for several reasons. (1) Taft and Grob reported that even pK_a values of 4-substituted pyridines are “poorly” fitted by σ_p (74JA1236). (2) Clarke and Rothwell noted that a Hammett plot of the rates of alkylation of substituted pyridines with alkyl bromide in nitromethane is better described by two lines: one for 3-substituted and one for 4-substituted compounds, respectively (60JCS1885). (3) Tomasik observed that pK_a of 3- and 4-pyridines and -pyridazines are better correlated, for each position, if +M and –M substituents are treated separately (77MI1). Using a single modified σ parameter such as σ^+ or σ^0 falls under the general criticism that continuous ranges of such constants are necessary for all para and meta substituents (59JA5343; 59RTC815) and dual substituent parameter (DSP) treatments would be more appropriate (68MI2; 73MI2).

$$\log(K/K_H) \text{ or } \log(k/k_H) = \rho_I\sigma_I + \rho_R\sigma_R$$

The DSP provides a better description of electronic effects (1) because an additional parameter always increases the precision of the statistical tests used in correlations, and (2) because the ρ_I and ρ_R values are consistent with the

chemical behavior. The ratio ρ_I/ρ_R is 3.16, 2.75, and 1.15 for the 2-, 3-, and 4-positions, respectively (77MI1), showing the importance of induction vs. resonance and the analogy between the 2- and 3-positions already mentioned.

If a single substituent parameter equation that is easier to handle and to represent graphically, or a DSP more precise and accurate, is employed, then the steric effect may be estimated by difference.

$$\text{steric effect} = \log(k/k_H) - \rho\sigma$$

$$\text{or (DSP) steric effect} = \log(k/k_H) - (\rho_I\sigma_I + \rho_R\sigma_R)$$

We will see in the next section that quaternization of azines and azoles has been used to test the applicability and validity of steric parameters, to show their conformational dependence, and to propose new steric parameters suitable for ortho positions.

B. NUCLEOPHILIC REACTIONS AT RING NITROGEN

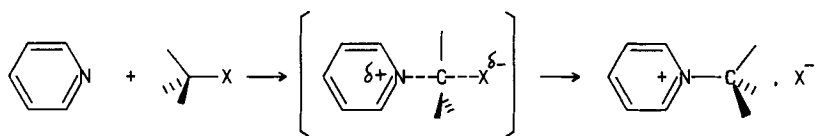
1. Quaternizations

The purpose of this section is not to update the two articles on the subject already published in this series by Duffin (64AHC(3)1) and by Zoltewicz and Deady (78AHC(22)71). We will rather focus on the problem of steric effects and treat all aspects related to that question.

a. *Mechanism.* Quaternization of aza-aromatic molecules is a subclass of the Menshutkin reaction, which involves a tertiary amine and an alkylating agent, giving a quaternary ammonium salt (Scheme 1).

This is a typical S_N2 reaction: (1) kinetics usually display clean second order; (b) when the reagent is chiral, inversion of configuration occurs at the asymmetric carbon (71ACS18); when the alkylating reagent is tertiary (*t*-butyl iodide) or even secondary (*i*-Pr iodide), E_2 elimination competes with aliphatic substitution (55JA1715; 76AJC1745).

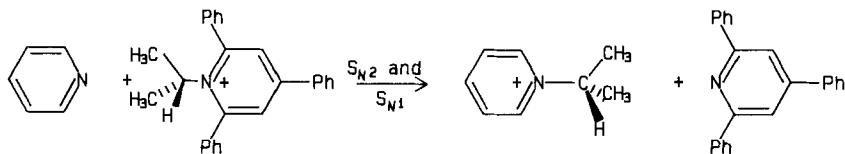
The nature of the transition state and its position along the reaction coordinate have been investigated by several methods. The reaction is said to be *early* when the degree of charge development (δ^+) on the nitrogen atom in the transition state (TS) is low compared to the final product. Experimental results consistent with this picture include solvent effects on the free energy of reactants and free energy of activation (75JCS(P2)623; 69CC1307), chlorine isotope effects (72JA1901; 79JOC889), the effect of pressure on the reactivity of bulky pyridines (75JA1778), comparison of rate constants with heats of reaction (76JA1468), and several Brönsted relations showing slopes $\alpha = 0.35 \pm 0.05$.



SCHEME 1

That steric effects can be used to estimate variation of TS structure along reaction coordinates has been proposed (76JA1260) and discussed (78JA2930; 81JA5915). A very complete kinetic and thermodynamic study of alkyl transfer to 3- and 4-substituted pyridines by Arnett and Reich shows that "the transition state is early as far as bond formation to the base is concerned but late in terms of bond rupture between the transferring alkyl group and the leaving group with solvent reorganization nearly complete (80JA5892)." This interpretation has been questioned (81CC421; 81JA5915). Deviations from the ideal S_N2 case occur under borderline conditions with special characteristics of reagents and reaction medium. The reaction is normally irreversible at ambient temperature, except in some cases with very bulky groups in the ortho position at higher temperatures (e.g., 2-*t*-butylpyridine with methyl iodide at 70–110° and above) (55JA1715). This reversibility has been developed for synthetic and mechanistic purposes (76JOC2621; 80T679; 84CSR47). The occurrence of an S_N1 mechanism was detected from rate constants (80TL2697) when pyridine displaced a 2,4,6-triphenylpyridine on an isopropyl group (Scheme 2).

b. *Reagents, Solvents, and Reaction Conditions.* Kinetic studies of quarternization related to steric effects have been run mostly with alkyl, benzyl, and vinyl halides. The frequently used methyl iodide or even ethyl iodide is preferred over the corresponding chlorides and bromides because they are liquid at ambient temperature or slightly above and therefore easier to handle. Dimethyl sulfate and methyl tosylate have also been used. The highly efficient alkyl fluorosulfonates (68CC1533; 69CC1389; 82S85) were employed for two purposes: (1) to estimate possible changes in the position of the transition state of S_N2 reactions (76JA1260; 78JA2930) and (2) alkylation under atmospheric pressure of 2,6-DTBP and 4-substituted derivatives **1a,b,c**



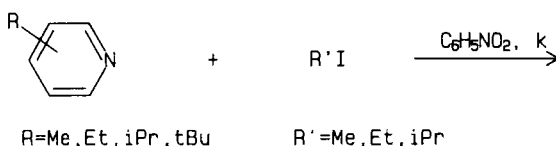
SCHEME 2

and 570/1 for the N-methylation of pyridine with methyl iodide in nitrobenzene compared to isopropyl ether (36JCS1353).

Quaternizations, in general, involve the transformation of neutral reagents to ionic products, and are best carried out in polar solvents. Since the reacting nucleophile is nonionic, protic solvents are not highly unfavorable. For example, going from acetonitrile ($D = 36.8$) to methanol ($D = 33.6$) lowers the rate only by a factor of 13.2 in the reaction $\text{DABCO} + (2\text{-bromoethyl})\text{benzene}$ or by 36 in the reaction $\text{Et}_3\text{N} + \text{CH}_3\text{I}$. Going from dimethylformamide (DMF) to methanol reduces the rate by a factor of 8.8 in the reaction of pyridine with benzyl bromide; this is interpreted from calorimetric studies as caused by solvation of the transition state in the dipolar aprotic solvent rather than by solvation of the reagents (71JOC1792). The most commonly used solvent in kinetic studies is nitrobenzene, probably following the original work of H. C. Brown. Polar aprotic solvents (acetonitrile, DMSO, DMF, and sulfolane) have been used more frequently since 1977.

Absolute rate constants vary notably from nonpolar to polar aprotic solvents, however, the changes in relative rate constants in different solvents are small. In a study on pyridine nitrogen reactivity with 3- and 4-substituted pyridines, Johnson *et al.* report that the ratio of rate constants of 4-NMe₂ over 3-COMe-pyridine ranges from 121 to 79.5 in the series nitrobenzene, nitromethane, methylene chloride, acetonitrile, and acetone (81JCS(P2)409); the relative ratio of 121/79.5 = 1.52 is equivalent to 0.18 log unit, a little larger than the commonly accepted error in LFER (0.10 log unit) (72MI1; 82MI1) and far below common values of steric effects from the S^0 scale for methyl ($S^0 = -0.73$) or *t*-butyl ($S^0 = -3.94$). The only exception in the work of Johnson is MeOH, which shows a leveling of reactivity, the ratio 4-NMe₂- to 3-COMe-pyridine being 1.43. In a study by Lund and Lund (73ACS383), the ratio of isomers N^1/N^2 obtained in quaternization of 3-*t*-butyl-6-dimethylaminopyrazine is remarkably solvent invariant: N^1/N^2 ranges from 63/37 to 62/38 in the series hexane, benzene, CCl_4 , acetone and acetonitrile. Only with ethers, such as dimethoxyethane and tetrahydrofuran (THF), was a small change observed. This solvent invariance of relative rates or isomer proportions (except with alcohol and ether) is important in the interpretation of mechanistic changes as revealed by an increase to the sensitivity of steric effects in heteroaromatic series (76JA1260).

c. *Azines, Azoles, and Benzo Analogues with One N Atom.* The title compounds have been, by far, the most widely studied. Qualitative and quantitative data allow one to understand well the mechanism of reaction and to predict to a reasonable extent the relative rates of reaction and the regioselectivities in di- and polyazines and -azoles as well as in aminoazines and azoles (ring vs. amino nitrogen).



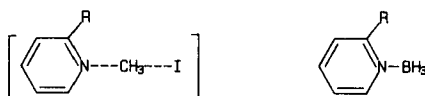
SCHEME 6

The first important quantitative paper on steric effects in quaternization of heteroaromatics was by Brown and Cahn (55JA1715). The reaction rate constants for reaction of 2- 3-, and 4-monoalkylpyridines with methyl, ethyl, and isopropyl iodides, determined in nitrobenzene at several temperatures (Scheme 6), are summarized in Table II.

For the same pyridine, the reaction rate decreases sharply from methyl to ethyl and further from ethyl to isopropyl iodide. This is in line with steric hindrance in S_N2 reactions well established by Ingold (57QR1). Introduction of a methyl group in a 3- or 4-position of the pyridine results in a small increase in rate with almost no variation as the substituent is changed from methyl to *t*-butyl; these variations closely follow pK_a values. The introduction of a methyl group in position-2 causes a rate constant decrease of 2.1, whereas an increase of 2 was expected from pK_a if no steric effect were present. The decrease in rate caused by steric strain is exponential going from 2-methyl to 2-*t*-butyl. The energy of activation shows a corresponding increase, while $\log A$ decreases slowly. Varying the 2-alkyl series while increasing the size of the

TABLE II
 pK_a AND RATE DATA FOR THE REACTION OF PYRIDINE BASES WITH ALKYL IODIDES IN
 NITROBENZENE SOLUTION

pK_a	RC_4H_4N	Methyl iodide		Ethyl iodide		Isopropyl iodide	
		10^6k	E_a	10^6k	E_a	10^6k	E_a
5.17	H	343	13.9	18.3	16.0	0.941	17.7
5.97	2-Me	162	14.0	4.27	16.5	0.0509	19.2
5.97	2-Et	76.4	14.2	1.95	16.6		
5.83	2- <i>i</i> Pr	24.5	14.8	0.555	17.1		
5.76	2- <i>t</i> Bu	0.080	17.5				
5.68	3-Me	712	13.6	40.0	15.5	1.73	17.4
5.70	3-Et	761		41.0		1.81	
5.72	3- <i>i</i> Pr	810		40.4		1.68	
5.72	3- <i>t</i> Bu	950		43.3		1.56	
6.02	4-Me	760	13.6	41.9	15.8	1.99	17.3
6.02	4-Et	777		42.1		2.01	
6.02	4- <i>i</i> Pr	767		42.2		1.98	
5.99	4- <i>t</i> Bu	757		41.9		2.00	



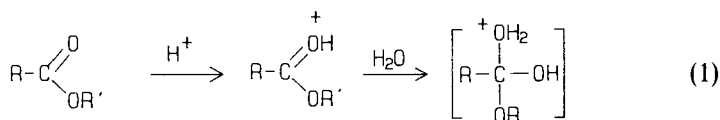
SCHEME 7

alkyl iodide results in a magnified decrease in rate and increase in E_a . The “telescopic” decrease in rate going from 2-methyl to 2-*t*-butyl was attributed to the possibility that the ethyl and isopropyl “rotate away” from the entering alkyl group, this rotation causing no reduction in strain in the *t*-butyl group. The concept of isomorphism, fully detailed in a later review paper (56JCS1248), was applied to this study. From a comparison with the addition compound with BH_3 (56JA5384), the strain in the TS of quaternization was estimated to be two-thirds of that in the final product (Scheme 7).

These quaternization rate constants of 2-alkylpyridines (Me—*t*-butyl) were correlated by Taft (53JA4538) with the steric parameters E_s .

$$\log(k/k_0) = \delta E_s, \quad \text{where } \delta = 2.06$$

This is interesting because E_s values were obtained from rates of catalyzed hydrolysis of aliphatic esters (52JA3126), and were originally devised for aliphatic series [Eq. (1)].



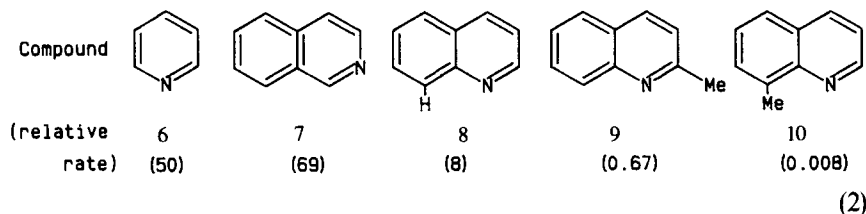
The importance of steric strain arising from benzo fusion in pyridines was first estimated by Packer and Wong (58JA905) in quaternization of methyl-substituted quinolines and isoquinolines. They used the “strained homomorph” concept of Brown (53JA1) to approximate strains existing in naphthalene compounds of similar geometry (e.g., 1-methylquinoline and 1-methylnaphthalene) (Scheme 8).

The relative rates of N-alkylation by methyl iodide of **7** and **8** relative to **6** suggest a steric effect of a *peri* hydrogen a little larger than that of the “comparable” 2-methyl [Eq. (2)]. Later a more precise estimation, using a Brönsted equation to estimate the electronic effect of the benzo, shows that the



SCHEME 8

peri hydrogen in **8** has the size of a methyl in position-2, "locked" by an adjacent 3-methyl, in a conformation where a hydrogen atom points toward the nitrogen (83T4209).



Homomorphs **9** and **10** of 2,6-dimethyl- and 2-*t*-butylpyridine show rate decreases, compared to **8**, of respectively 11.9 and 1000. Here again the changes in rate constants are associated with large increases in ΔH^\ddagger and small variations in $T \Delta S^\ddagger$.

Deady *et al.* estimated the effect of benzo fusion in five-membered rings (73AJC1949; 74AJC1221). They reported rates of N-methylation of azoles **11**, isozoles **12**, and benzoanalogues **13**–**15**. The order of reactivity is X = NMe > S > O in both series, with derivatives **11** being more reactive than **12** for each heteroatom X (Scheme 9).

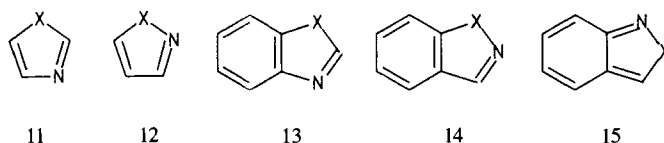
There is a good Brønsted plot for methylation of these derivatives against pK_a . From the available points (thiazole–benzothiazole; 1-methylimidazole–1-methylbenzimidazole) it appears that benzo fusion does not cause a deviation from the Brønsted plot due to steric strain, unlike in the azine series. Results by Behera *et al.* on quaternization of thiazole and other benzoazoles and benzoazines involve steric effects but they have not been separated quantitatively from electronic effects (73JOC2164). Deady and Stillman have also shown the relative importance of steric effects due to benzo fusion in quaternizations of pyridine, thiazole, isothiazole, and their benzo analogues by comparing the reactivity of pairs of reagents of increasing size with alkyl iodide in order to magnify the benzo fusion effect (Table III) (76AJC1745).

Coppens *et al.* (63BSB25) studied the quaternization of monohalogenopyridines with methyl iodide. Comparing the activation energies of reaction to

TABLE III
RELATIVE QUATERNIZATION RATES OF HETEROCYCLIC PAIRS
WITH ALKYL IODIDES^a

Heterocyclic pair	MeI	EtI	<i>i</i> PrI
Pyridine/quinoline	9.7	15	55.1
Thiazole/benzothiazole	5.8	6.4	8.5
Isothiazole/2,1-benzisothiazole	1.1	1.2	

^a In sulfolane at 65°C.



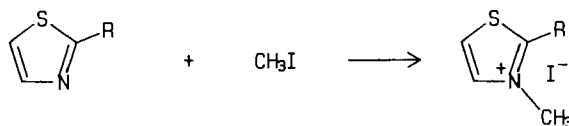
SCHEME 9

the pK_a values, they suggest the following values for the compression energies of ortho substituents: Cl = 0.17, Br = 0.65, CH₃ = 0.50 kcal mol⁻¹. Tokura and Kondo (64BCJ133) observed a very small decrease in rate constants from 2-methylpyridine (9.5) to 2,6-dimethylpyridine (7.95) and an even more surprising decrease in activation energy (17.4 and 14.4 kcal mol⁻¹) in sulfur dioxide. Hudson and Withey (64JCS3513) reported, from reaction between ethyl methanesulfonate and several methylpyridines in water, that the Brønsted α value is very small ($\alpha = 0.11$) and that ortho-substituted pyridines give two parallel lines below the Brønsted equation, one for the derivatives having a methyl in position-2 and another for the derivatives having two methyl groups in position-2 and -6. The smaller steric requirement of deuterium compared to hydrogen was confirmed in quaternization of methylpyridines by Brown and McDonald, who studied the relative reactivities of CD₃ and CH₃ on the pyridine nucleus and found no change in position-3 and -4 and an enhanced reactivity in the 2-position (66JA2514).

Later, Balaban *et al.* showed that the accelerating secondary isotope effect obtained on replacing two α -CH₃ groups by two CD₃ groups consists approximately of equal amounts of steric and electronic components (82JCR(M)559, 82JCR(S)44).

Quaternization of two series of 2-alkylthiazoles with methyl iodide shows a completely different behavior (Scheme 10). With the α -series (Me, Et, *i*Pr, *t*-Bu), the rate decrease is correlated with the Taft E_s parameter (67BSF4502) as already observed with pyridines. With the β -series (Et, *n*Pr, *i*Bu, neopentyl) the rate decrease is very small compared to that suggested by E_s parameters (Fig. 2), e.g., the neopentyl group in position-2 of the thiazole appears a little more bulky than the 2-ethyl but far less than the *t*-butyl, whereas the neopentyl on the E_s scale is the largest of the α - and β -series groups.

Both the good correlation of rates with E_s for the α -series and the insensitivity for the β -series have been tested further to better understand the



SCHEME 10

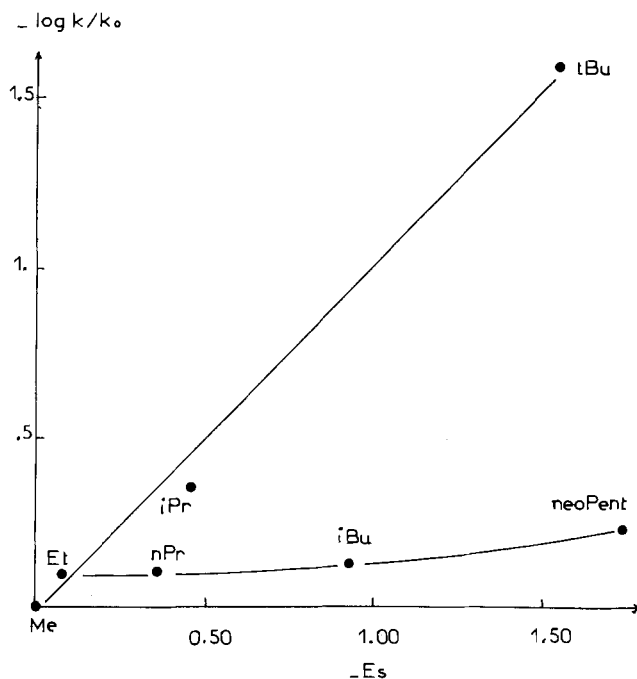
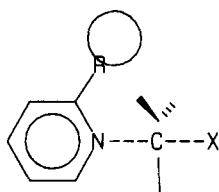


FIG. 2. Plot of E_s vs. $\log(k/k_{Me})$ in quaternization of 2-alkylthiazoles by ICH_3 .

mechanism of quaternization and of S_N2 reactions. The slope δ of the equation $\log(k_R/k_{Me}) = \delta E_s$ was shown to measure the sensitivity to steric effects of quaternization of azines and azoles having *o*-alkyl substituents (α -series), i.e., to be related to gross geometrical changes like the size of the ring, six-membered rings being more prone to steric strains than five-membered ones, and the associated external angles in the ring (72TL3857; 79JCS(P2)398).

The excellent correlations ($R \geq 0.998$) obtained with the α -series in quaternization of heteroaromatics were used to estimate possible geometrical variations in the transition state of the S_N2 reaction (Scheme 11).

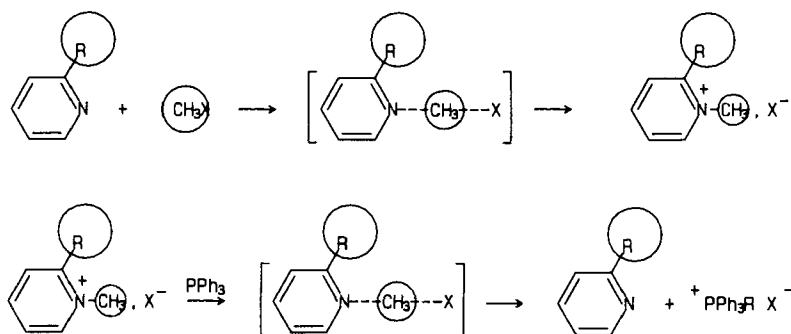


SCHEME 11

Keeping constant the heterocycle, the alkylating group, and the R series, but varying the leaving group, no significant modification in the sensitivity to steric parameters ($\delta = 1.03$) is observed on changing tosylate for iodide (a factor of 1/3 in reactivity). However, there is a notable variation ($\delta = 0.69$) on changing fluorosulfonate for iodide (a factor of 10^4). This was proposed as experimental evidence of the Hammond postulate (55JA334) of the TS being closer to reagents (longer C—N bond and smaller steric effects) with a smaller ΔG^\ddagger (better leaving group), provided the difference in leaving group ability is large enough (76JA1260). The sensitivity to steric effects estimated from δ has also been used in comparing the alkylation of pyridine derivatives by methyl iodide to the dealkylation of pyridinium iodides by triphenyl phosphine (76JOC2621): The steric strain in this quaternization is twice as large as the strain released in dequaternization of pyridine (76JOC2621) and the quinolines (79AJC1735) (Scheme 12).

A mechanistic study by Deady and Korytsky, which showed that dealkylation is exactly the reverse of the alkylation reaction (79TL451), implies, according to the principle of microscopic reversibility, that the amount of strain in the TS for quaternization is two-thirds of that in the final quaternary salt, in close agreement with the early estimate by Brown. The ratio of substituent steric effects is 3/1 for disubstituted pyridines in methylation vs. demethylation. Because of smaller sensitivity to steric effects in thiazoles, steric acceleration in the reverse reaction is small (76AJC1745; 79BSF(2)484).

While good δE_s correlations within α -substituted series were found in mechanistic studies, the reason for nonapplicability of E_s parameters to a β -series in the quaternization of thiazoles was not experimentally determined. There are two possible reasons for this nonapplicability. (1) The Taft E_s parameters are not solely a measure of steric effects, but rather also contain inductive, resonance, and other effects and must be corrected and more precisely redefined. (2) The Taft E_s parameters do measure steric effects, but,



SCHEME 12

depending on the nature of the reaction, a nonsymmetrical substituent may have a completely different orientation and steric behavior.

Point (1) was given as the usual explanation for poor correlations of reactivity data with E_s ; this was the origin of modified E_s parameters. Hancock proposed E_s^c constants, corrected by a hyperconjugation factor (h) and the number of α -hydrogen atoms (n) of the substituent (61JA4211).

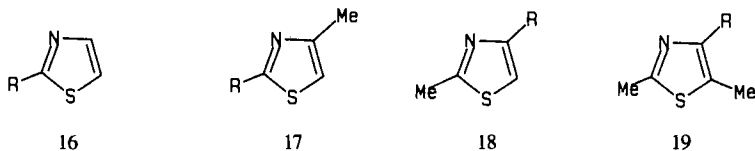
$$E_s^c = E_s - h(n - 3)$$

Talvik and Palm made a similar analysis, taking into account hyperconjugation of α -CH and α -CC bonds (710R445), and defined E_s^0 constants:

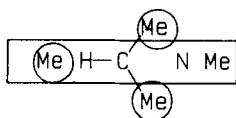
$$E_s^0 = E_s + 0.33(nH - 3) + 0.13nc$$

Charton (75JA1552) and Dubois *et al.* (78T3553) found no improvement by using E_s^c . Shorter made pertinent objections concerning better correlation coefficients R obtained when using E_s^c (72MI1). Dubois *et al.* proposed revised Taft constants E_s' ; these parameters are notably different from E_s values for very bulky groups, but similar to E_s for most groups, such as those of the β -series. Indeed, using E_s^c , E_s^0 , and E_s' resulted in no improvement of the correlation for α - and β -alkylthiazole quaternizations. Regarding point (b), Charton showed that E_s is a linear function of van der Waals radii, independent of electronic effects, when groups of different symmetry (CH_2X , CHX_2 , CX_3) are considered (69JA615). Therefore, the inapplicability of E_s to heteroaromatics for all alkyl groups is probably of conformational origin. Several authors have recognized the importance of conformational states in the use of steric parameters for alkyl groups (83MI2). One bit of evidence comes from the quaternization of alkylthiazoles: To show experimentally that the differences in behavior of CH_2R groups are due to conformational differences, the series Me, Et, *i*Pr, and *t*-Bu, (which gives excellent linear correlations) was studied in modified conformational states (73JA3807) (Scheme 13).

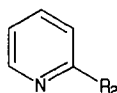
For series 16, 17, and 18 ($\text{R} = \text{Me}$, Et, *i*Pr, *t*-Bu), the equation $\log(k/k_0) = \delta E_s$ holds, with δ values being 0.96, 1.57, and 1.63, respectively; for each relation, the correlation coefficient R is excellent ($R \geq 0.997$). For these series, the barriers to rotation of the alkyl groups are very small, resulting in a good



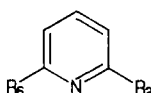
SCHEME 13



SCHEME 14



20



21

SCHEME 15

linearity of the δE_s plot, and the increased sensitivity to steric effects (δ) is not related to the geometry of the heterocycle but to the narrowing of the "reaction window" (82TL3879). When a methyl group is introduced in position-5 (19), it prevents free rotation of R and increases the population of the conformer, with the bulkiest side away from the 5-methyl (Scheme 14). This results in a strong curvature of the δE_s equation with the nonsymmetrical ethyl and isopropyl groups behaving as if they are more bulky than expected (73JA3807).

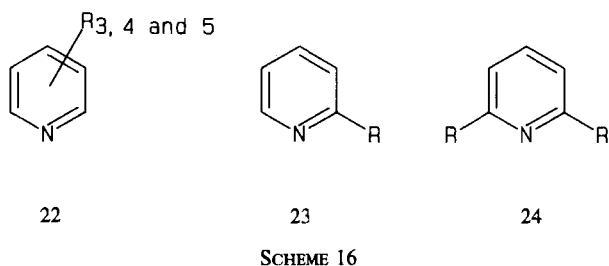
Evidently, E_s parameters cannot be used when strong conformational preferences exist, and for heteroaromatics ortho-steric parameters are required.

For describing the nucleophilicity of 2-alkylpyridines, Popov and Gelbina (77OR145) proposed ortho-steric parameters E_N , but values given were limited to the α -alkyl series where good correlations are usually observed.

Deady and Zoltewicz studied the influence of a larger set of substituents on the kinetics of quaternization of derivatives **20** and **21** including alkyl and functional groups R in position-2 and/or R-6 (72JOC603) (Scheme 15). As expected, the kinetic results are poorly correlated with pK_a values. Separate correlation lines were required for 2-substituted and 2,6-disubstituted pyridines. It was suggested that steric effects are superimposed on electronic effects, and that steric effects are nearly constant for ortho substituents like NH_2 , Me, Cl, Br, and CN, but are more important for Et, CH_2Ph , 2-pyridyl, and CO_2Me .

A detailed correlation analysis of the N-methylation of pyridines was later carried out by Schaper on a complete series of 83 azines (**22–24**) (Scheme 16) and diazines (78AP641; 78AP650); 3-, 4-, and (or) 5-substituted pyridines **22** give:

$$\log k = 0.341 \, pK_a - 1.685 \quad (r = 0.986)$$



while 2-substituted pyridines **23** give a parallel Brönsted line with a poor correlation:

$$\log k = 0.266 \text{ p}K_a - 2.297 \quad (r = 0.913)$$

The best description of ortho- and non-ortho-substituted pyridines **22** and **23** [excluding 2-*t*-butyl, 2-Et₂N, 2-(2-pyridyl), and 8-methylquinolyl] is

$$\log k = 0.312 \text{ p}K_a - 0.879R(2) - 1.58 \quad (r = 0.967)$$

$R(2)$ is a "dummy parameter," being 1 with a substituent in the 2-position and zero with no substituent in the 2-position; the same type of equation was proposed for 2,6-disubstituted pyridines with $R(6)$ being defined analogous to $R(2)$.

$$\log k_{\text{rel}} = 0.295 \text{ p}K_a - 0.880R(2) - 0.804R(6) - 1.521$$

The analysis is based on the implicit assumption that steric effects of ortho groups are nearly constant except for very bulky groups having special structures (e.g., *t*-butyl) for which an additional dummy parameter D is required. The complete equation is thus

$$\log k_{\text{rel}} = 0.297 \text{ p}K_a - 0.898R(2) - 0.722R(6) - 2.354D - 1.528$$

Schaper notes, however, that this analysis is not in agreement with earlier studies using E_s [i.e., in Fig. 3, where E_s correlates well with the Me-*t*-Bu series (line A), not with *n*-C₃H₇ and *i*-C₄H₇]. According to Schaper all alkyl groups are nearly constant (line B), *t*-butyl being a maverick.

Clearly neither analyses is fully satisfactory and ortho-steric parameters are needed to incorporate all substituents in a single homogeneous series. In fact, ortho-steric parameters exist; they have been proposed by Taft (E_s^0) from the esterification of benzoic acids (56M1), by Kindler from the alkaline hydrolysis of cinnamates (28LA278), by Farthing and Nam (σ_s) from the ionization constants of benzoic acids (50MI1), and by Hussey and Diefendorfer (S. F.) from the polarography of 2-substituted phenyl halides (67JA5359). However, Charton concluded from a statistical analysis that all these param-

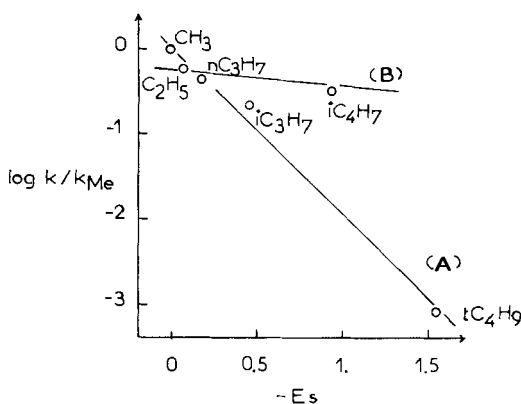


FIG. 3. Plot of $\log(k/k_{Me})$ in quaternization of 2-alkylpyridines in MeOH vs. E_s (78AP650).

eters are independent of the size of the groups and are mostly (if not completely) electrical effect parameters (71MI2).

A new scale of ortho-steric parameters S^0 was determined by Berg *et al.* from the N-methylation of pyridines (80JCS(P2)1350). It is based on the fact that all ortho-substituted pyridines fall below the Brönsted line obtained under the same conditions with non-ortho-substituted pyridines (Fig. 4).

For each ortho substituent, the deviation from the reference line is far greater than the error in the slope of this line. A steric parameter for each

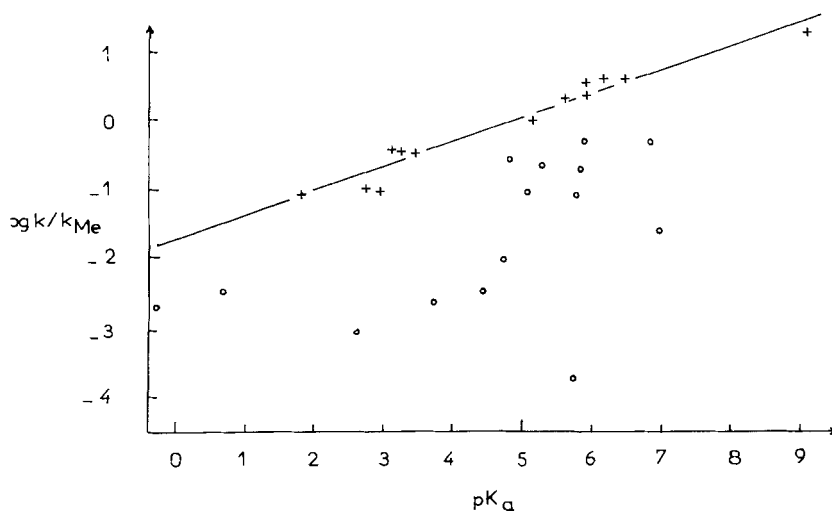


FIG. 4. Relative rate constants for alkylation of pyridines by ICH_3 in CH_3CN vs. pK_a . \bigcirc , ortho substituents; +, nonortho substituents

substituent is calculated from the equation

$$S^0 = \log(k/k_H) - (\alpha pK_a + C)$$

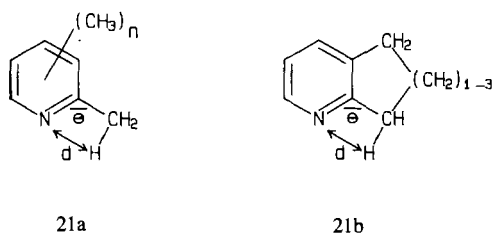
The S^0 parameters depend very little on the solvent (DMSO, $C_6H_5NO_2$, CH_3CN , and acetone). There is a complete lack of correlation between S^0 and their electronic effects, but good agreement of S^0 with other experimental estimations of the size of substituents (77AG(E)429). The difference in behavior of S^0 and E_s comes from the difference in strain, between ground and TS in azine quaternization (S^0) and acid-catalyzed hydrolysis of esters (E_s), of substituents having a different symmetry. Clearly S^0 should be preferred to E_s in correlating reactivity of aromatics and heteroaromatics. A listing of S^0 parameters, with additional values, is given in Section II.E. However, using different scales of steric parameters for aliphatic (E_s) and heteroaromatics (S^0) structures may appear to be a narrow methodology. A general scale of steric constants based on geometrical parameters needs to be defined. Hence, the (upsilon) scale of Charton where the v parameters were defined by

$$v_X = r_{VX} - r_{VH} = r_{VX} - 1.20$$

with r_{VH} and r_{VX} being the van der Waals radii of hydrogen and of a symmetrical top substituent, respectively (75JA1552). For nonsymmetrical top substituents, addition v parameters were obtained from kinetic data of acid-catalyzed ester hydrolysis and esterification of carboxylic acids, which had been used by Taft to define E_s (75JA1552; 76JOC2217). Not surprisingly, the correlation between v and E_s is excellent, which means that v parameters are not basically different from E_s ; they have the same advantages and limitations. More generally, no single parameter scale (one substituent, one parameter) will ever be of general applicability, whether its origin is empirical, physical, topological, or theoretical (83MI2).

However, since steric effects are basically geometrical in character, efforts have focused in the direction of selecting one or several geometrical parameters. Seeman and co-workers (81JA5982) correlated nonadditive kinetic effects due to substitution and annelation in **21a** and **21b** with parameters d and Θ derived from MINDO/3 ground-state molecular geometries (Scheme 17). Extending this study they made an important contribution to the quantitative analysis of steric effects in quaternization by comparing not only LFER and semiempirical MINDO/3 methods, but also geometrical and overlapping models (84JA143).

In series **22a**, where one α -substituent is methyl or cycloalkyl, they compared the kinetic nonadditivity parameter $S = k_{rel}/k_{calc}$ (k_{calc} using LFER) with geometrical parameters Θ and d_{NH} calculated for the ground state by



SCHEME 17

MINDO/3 as in **21a** or **21b** (Scheme 18), and with the steric ortho parameters S^0 .

$$S = 5.16d_{\text{NH}} - 12.4 \quad (r = 0.983)$$

$$S = -10.0 \cos \theta - 1.56 \quad (r = 0.971)$$

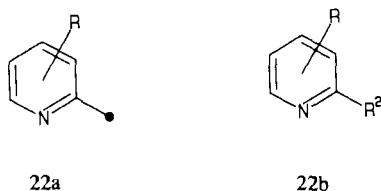
$$\log(S) = 0.859S^0 + 0.515 \quad (r = 0.950)$$

Then they correlated S^0 in **22a** and **22b** (where R^2 is nonsymmetrical or where molecules are 2,6-disubstituted) to the nitrogen's accessibility defined by solid angles from a point $P = 1.75 \text{ \AA}$ from the pyridine nitrogen atom in connection with the Wipke and Gund (74JA299; 76JA8107) steric congestion model. They also correlated S^0 with radical overlaps Σr^* between the incoming methyl and substituents in positions-2 and -6, according to the model used by Sternhell *et al.* **23** (Scheme 19) to describe hindered rotations in biphenyls (80JA5618). This is an interesting contribution to the unified description of steric hindrance in intra- and intermolecular processes.

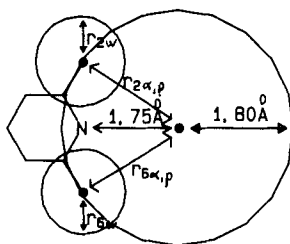
$$\Sigma r^* = (r_{2w} + 1.8 - r_{2\alpha,p}) + (r_{6w} + 1.8 - r_{6\alpha,p})$$

$$S^0 = -2.33 \Sigma r^* + 1.67$$

All these correlations in fact involve only a single geometrical parameter. The interatomic distance d (as in the Sterhnell model) is one element of the van der Waals interaction E_n , e.g., in the Lennard-Jones potential (67JA7036)



SCHEME 18



23

SCHEME 19

$E_{nb} = a/d^{12} - b/d^6$; the angle Θ is included in the Hooke's law of bond angle deformation E_{Θ} .

$$E_{\Theta} = \Sigma k/2(\Theta - \Theta_0)^2$$

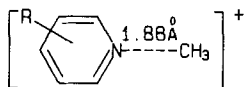
A complete treatment must include all the geometrical modifications occurring during the reaction that make up the total energy of the TS. This can be approximated by semiempirical quantum calculations or by molecular mechanics.

Schug and co-workers found a good correlation between the calculated activation energy [ΔE -(calc)] and the logarithms of the methylation rate constants for 37 alkyl-substituted pyridines and 6 hetero-substituted pyridines (83JOC4892), including 30 ortho derivatives.

$$\log k_{rel} = -0.093 - 0.178(\Delta E_{calc}/RT)$$

Calculations of energy differences between the TS model and the completely optimized ground-state molecule were carried out with the semiempirical all-valence electron (MINDO/3) self-consistent force field procedure; the TS model was constructed by placing a CH_3^+ moiety 1.88 Å from the pyridine nitrogen and completely optimizing the $(\text{CH}_3\text{-substrate})^+$ supermolecule (Scheme 20).

Berg and Gallo (83ACS(B)661) calculated the $\text{S}_{\text{N}}2$ transition-state structures for the Menshutkin reaction between 2-alkylpyridines or -thiazoles and CH_3X ($\text{X} = \text{I}$ and SO_3F) by the Allinger 1973 (MM1) force-field method. The preferred model of TS results in $r_{\text{C-N}} = 1.81 \pm 0.01$ Å. Experimentally found differences in steric energies are in agreement with molecular mechanics

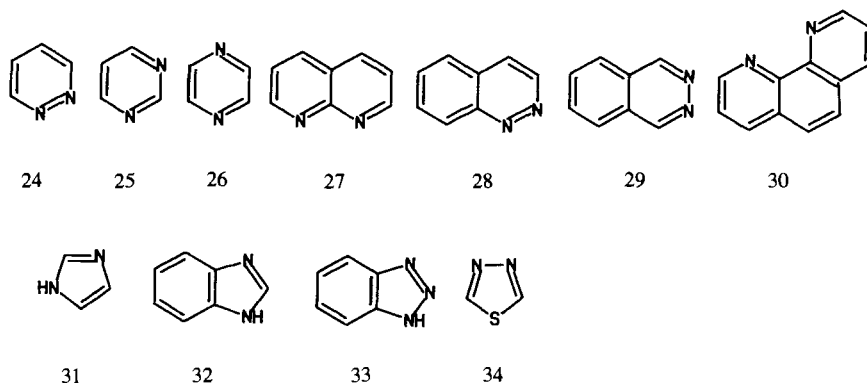


SCHEME 20

calculations, consistent results being obtained with nucleophiles of different geometries (pyridines and thiazoles). The scope and limitations of molecular mechanics will be further discussed in Section III.

d. *Di- and Polyazines and -azoles.* In this series, reactivity studies cover not only rate constants for quaternization but also regioselectivity corresponding to relative rates on two different nitrogen atoms. Since reactions are usually under kinetic control, the regioselectivity $\%N/\%N'$ is a direct measure of k/k' on nitrogen atoms N and N'. Quantitative studies of steric effects have been carried out on di- and polyazines **24**–**30**: pyridazines **24** (67ACS1067; 72JA(94)2765; 72T1983; 72TL189; 72TL3857; 73ACS383), pyrimidines **25** (72JA(94)2765; 72TL189), pyrazines **26** (71JA(90)5475; 72JA(94)2765; 72TL189), naphthyridines **27** (69CC56; 72T1983; 85JOC2972), cinnolines **28** (71JCS(C)3088; 72JA(94)2765; 79IJC(B)359), phthalazines **29** (72JA(94)2765; 72TL189), phenantrolines **30** (81AJC163); and on di- and polyazoles **31**–**34**: imidazoles **31** (64JCS3513; 82TL3879), benzimidazole (indazole) **32** (73AJC1949; 73JOC2164; 75JCS(P2)4360), benzotriazole **33** (75JCS(P2)4360), and thiadiazole **34** (72TL3857; 73ACS391) (Scheme 21).

Keeping in mind that the introduction of a nitrogen atom in the pyridine ring results in a lowering of the pK_a in the order para > meta > ortho (pyridine = 5.23, pyrazine = 0.65, pyrimidine = 1.31, pyridazine = 2.33), quantitative measures of steric (and electronic) effects can be extrapolated from the quaternizations of azines and azoles to those of di- and polyazines and -azoles. In addition, a specific consequence of two nitrogen atoms in ortho positions in a ring is the possible occurrence of an α -effect, resulting in super nucleophilicity. Figure 5, from a study by Zoltewicz and Deady, summarizes these observations (72JA(94)2765). The Brönsted correlation incorporates pyridine, substituted pyridines, pyrimidine **25** and pyrazine **26**; a modest



SCHEME 21

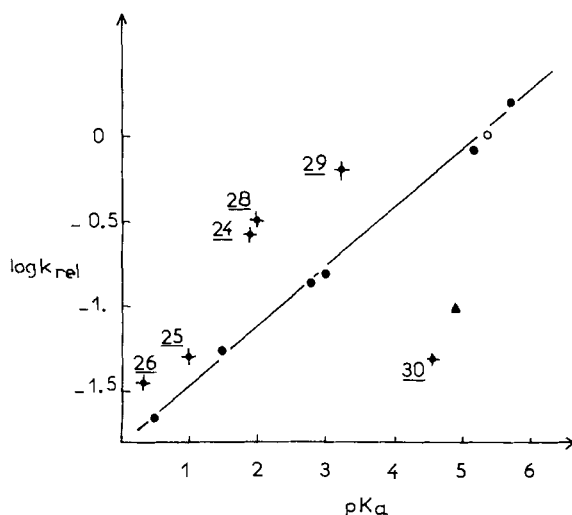
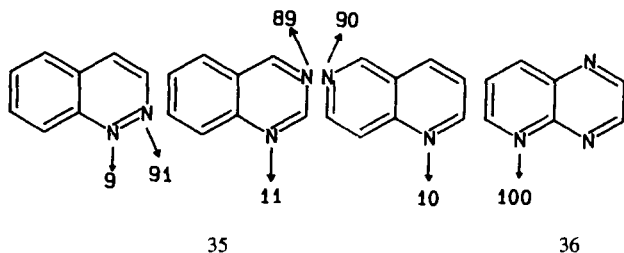


FIG. 5. Bronsted correlation, including substituted pyridines (●), quinoline (▲), isoquinoline (○), and diazines (+).

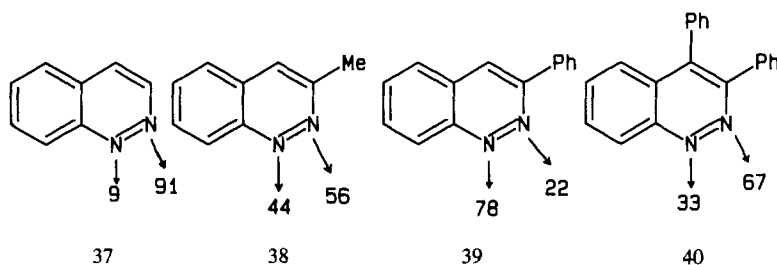
α -effect (rate increase by a factor of 4) occurs with pyridazine **24a**, phthalazine **29**, and cinnoline **28**, while rate decreases due to steric effects are observed with quinoline (~ 8) and phenanthroline (**30**) (~ 12).

The problem of regioselectivity, which was assigned earlier by chemical (64AHC(3)1) and later by NMR (67ACS1067; 71JA(90)5475; 78AHC(22)71) analysis of products, can be rationalized qualitatively by structural factors. Thus, in Eq. (3) (Section II,B,3,a) the ratio of isomers obtained in cinnolines (71JCS(C)3088), quinazolines **35** (72JA(94)2765), 1,6-naphthyridines (69CC56), and triazanaphthalenes **36** (72T1983) is understandable in terms of a "quinoline" peri-steric interaction and of the larger deactivation by a nitrogen atom in the same ring than by one in an adjacent ring, as in **36** (Scheme 22).

Introduction of a substituent into the ring complicates the problem; it changes the isomeric ratio. For example, in **38** and **39** (71JCS(C)3088) this



SCHEME 22. Rate constant derived from product ratios.



SCHEME 23

ratio depends mostly on the relative size of a methyl and of a phenyl group, and on the reduced sizes of two adjacent twisted phenyls in **40** (Scheme 23). It creates a regioselectivity where there was none because of symmetry (**24–27**, **29–34**).

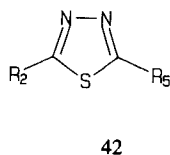
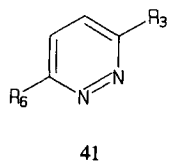
A general method for solving the problem and determining the position of alkylation in polyaza heterocycles was proposed by Deady and Zoltewicz (71JA(90)5475; 72T1983): The reactivity of an annular nitrogen atom toward a methylating agent is estimated by algebraic addition of substituent rate factors derived from kinetic studies on model compounds (Table IV).

The isomer ratios estimated for a series of pyrazines, pyridazines, and pyrimidines are in good agreement with experiment (72T1983); they provide not only reasonable predictions of isomer ratios of quaternization products but also a method for rectifying many of the previously contradictory statements in the literature.

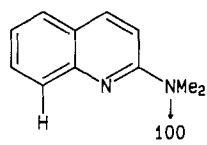
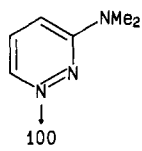
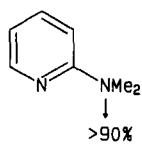
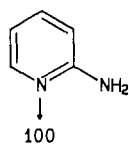
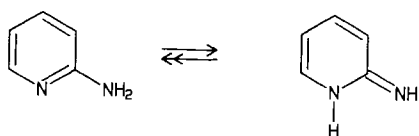
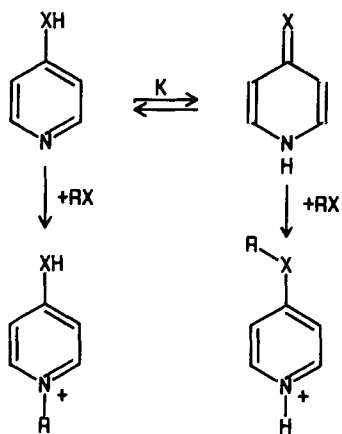
The rate factors are, however, complex; they are composed of electronic

TABLE IV
SUBSTITUENT RATE FACTORS (LOGARITHMIC
VALUES) FROM *N*-METHYLATION OF PYRIDINE
DERIVATIVES BY METHYL IODIDE IN DMSO TO BE
USED FOR PREDICTING THE REGIOSELECTIVITY IN
POLYAZINES QUATERNIZATION

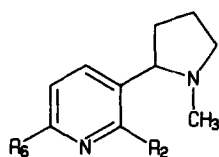
Substituent	Position		
	Ortho	Meta	Para
H	0	0	0
NH ₂	0.09	0.59	1.55
Me	−0.42	0.22	0.39
Et	−0.77	0.22	0.34
NHAC	−2.09	−0.48	0.27
Cl	−2.41	−0.86	−0.53
Co ₂ Me	−2.08	−0.85	−1.04
CN	−2.66	−1.28	−1.52



SCHEME 24



SCHEME 26a



SCHEME 26b

effects in meta and para positions (related to pK_a or to appropriate σ -constants) and of electronic and steric effects in ortho positions. Electronic effects will change little with the size of the electrophile, but steric effects will, as previously shown by the sensitivity of steric effects (δ -constant) to geometrical parameters. A more precise, but less easy to handle, equation is therefore

$$\begin{aligned} \%N-R/\%N'-R &= k/k'' = \text{antilog}(\alpha pK_a + \delta S^0) \\ &= \text{antilog}(\rho_I \sigma_I + \rho_R \sigma_R + \delta S^0) \end{aligned}$$

For substituents having the same electronic effect but very different size the equation shortens to

$$\log(\%N-R/\%N'-R) = \delta S^0$$

This can be applied to 3,6-dialkylpyridazines (**41**) (72TL3857; 73ACS383) and to 2,5-dialkyl-1,3,4-thiadiazoles (**42**) (72TL3857; 73ACS391) (Scheme 24).

e. *Ring vs. Substituent Heteroatom Reactivity.* The general problem of ambident reactivity is raised when the exo heteroatom is directly bonded to the ring. The topic is more complex than the regioisomerism in di- and polyazines because each reactive heteroatom may be involved in a protomeric equilibrium (76M11) (Scheme 25).

Quantitative estimations of structural effects are simplified for molecules existing mostly under one protomeric form, such as aminopyridines (Scheme 26).

Mostly qualitative explanations have been advanced to account for the observed results (71LA12). Aminopyridine (**43**) quaternizes only at the ring nitrogen, whereas the more bulky (cf. S^0 constant) dimethylamino group hinders the ring nitrogen and gives more than 90% alkylation at the exo nitrogen in **44** and 100% in **46**, where the peri hydrogen makes an even higher ortho-ortho steric effect. Similarly, NMe_2 shifts the reaction to N-1 in **45** (Scheme 26a).

An interesting study of conformationally mobile systems involves iodomethylation of nicotine derivatives **47**, where steric effects of substituents at position-2 and -6 modify the alkylation rate at the pyridine nitrogen and at the two nitrogens (N' trans and N' cis) of the pyrrolidine conformers (80JA7741; 81JOC3040) (Scheme 26b).

This has been analyzed in terms of Curtin-Hammett and Winstein-Holness equations (83CRV84).

2. Dequaternizations

Quaternary salts of heteroaromatic amines are stable derivatives and only during the 1970s have synthetic methods been proposed to achieve dealkylation using polar aprotic solvents such as hexamethylphosphoramide (HMPA)

(73JOC1961; 74SC183), DMF (72S702; 73CC32) with (or without) tertiary amines (72S702), and soft nucleophiles (75SC119; 76JOC2621). The reaction is interesting for three major topics: (1) temporary activation of the heteroaromatic ring; (2) fundamental studies of the TS in S_N2 reactions; and (3) transformation of primary amines into other functionalities via pyrylium salts. Steric effects have played a determining role in studies (2) and (3). Topic (2) has been developed in Section II,B,1; point (3) concerns a three-step procedure, which will be further discussed with respect to mechanistic (Section IV,C) and synthetic (Section V) implications.

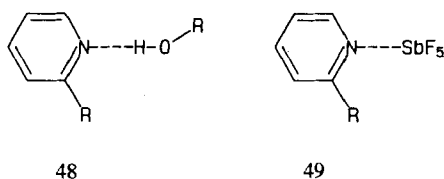
3. *Ring Nitrogen Complexes and Reactions with Electrophiles*

Steric effects occurring during the interaction between the nitrogen atom of aza-heteroaromatics and electrophiles will be much dependent upon the size of the electrophile.

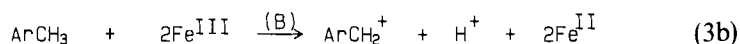
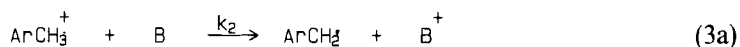
a. *Proton Acids.* Values of pK_a for solutions are little affected by the steric effect of ortho substituents, except for very bulky 2,6-disubstituted pyridines and similar compounds (cf. Section III,B,1). A close examination of pK_a changes in heteroaromatics with one ortho substituent shows a decrease of ~ 0.20 pK_a from methyl to *t*-butyl with pyridines (55JA1733), thiazoles (67BSF4502), and pyrazoles (68BSF5009). This is opposite to what is expected from electronic effects, but compatible with steric hindrance to solvation as revealed by protonation enthalpies and entropies for thiazoles (66ACS1314) showing the distinctive behavior of the ortho-*t*-Bu derivative, compared to the all mono-, di-, and trimethyl derivatives.

Steric effects will also be small in hydrogen-bonded complexes with acidic solvents, such as CH_3OH (84CP327), $CHCl_3$ (74MI2; 75JMR166), or phenols (77JCS(F)1326). This implies that the solvent basicity (Donicity) character of heteroaromatic solvents [as in the scales D based on the ν_{XH} shift of a proton-donor solvent (74OR121; 76JCS(P2)1627), or in the scale β defined by Kamlet and co-workers from solvatochromism of indicators (83JOC2877)] will be much less affected by steric strains (48) than other solvent scales like the Gutman donor number (DN) (49) (77CT255). The latter corresponds to a complex with a Lewis acid (Scheme 27).

Rates of proton transfer from radical cations to pyridine bases are a little more sensitive to steric effects than are equilibria for the corresponding pK_a values of the bases, as shown by Kochi *et al.* (84JA7472). The rate-determining step [Eq. (3a)] is the oxidative conversion of methylbenzenes by iron(III) complexes in the presence of these bases [Eq. (3b)].



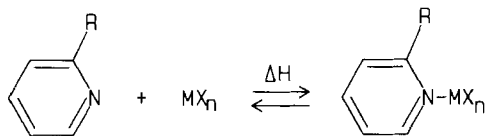
SCHEME 27



b. *Lewis Acids*. Early work on the importance of steric strain in addition compounds between pyridine derivatives and Lewis acids was carried out by H. C. Brown and his group (72MI2) (Scheme 28). The strength of pyridine and 2-alkylpyridines with reference acids of increasing steric requirements is clearly shown in Fig. 6 with $\text{CH}_3\text{SO}_3\text{H}$ (55JA1727), BH_3 (56JA5384), BF_3 (55JA1733), and BMe_3 (56JA5378).

According to the concept of homomorphism, this behavior may be extended to other Lewis acids and metal alkyls, such as AlCl_3 , BCl_3 , SnCl_4 , SnCl_5 , and BeEt_2 , which give adducts with heteroaromatics. For example, adducts with many Lewis acids are more difficult to form in the series pyridine, isoquinoline, quinoline, acridine. Seeman and co-workers (83JOC2399) have observed an excellent correlation between MINDO/3-calculated relative activation energies for methylation of 25 alkyl-substituted pyridines and Brown's experimental heats of trifluoroboration. Berthelot and co-workers (84JCP327) have shown for a series of pyridines a good correlation between ΔH of formation with BF_3 and ν_{OH} of association with methanol; deviations observed for ortho substituents are highly correlated with the S^0 parameters. Therefore, quantitative results obtained in quaternizations may be extrapolated to Lewis acids.

c. *Metal Ions*. Coordination complexes of heteroaromatics with metal ions are legion, but only recently have quantitative studies of the importance



SCHEME 28

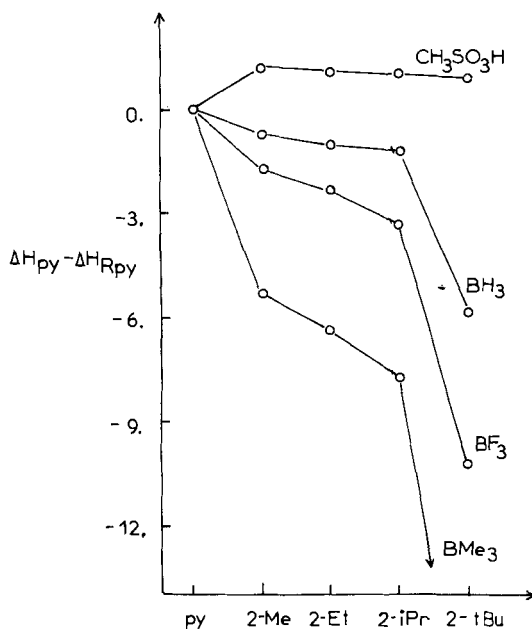
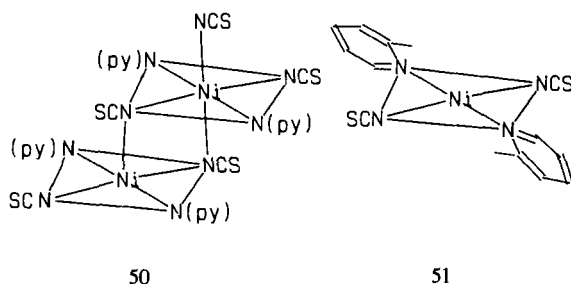


FIG. 6. Relative strengths of pyridine and 2-alkylpyridines with reference acids of increasing steric requirements.

of steric effects in these complexes been reported. The problem is difficult because steric strains not only lower the complexation constant with the metal or reduce the rate of displacement of ligands on the metal, but they also change the stoichiometry and in some cases the stereochemistry of the complex.

Typical examples of changes in stoichiometry and in stereochemistry of the complexes are the following. 3,5-Dimethylpyrazole (L) forms ML_4X_2 complexes ($M = Co, Mn, Ni, Zn$) whereas the number of ligands (L) is six with pyrazoles having one or no methyl substituent in position-3 or -5 (76MI2). Copper(I) complexes with methylpyridines exhibit different stoichiometry and stereochemistry; 3-picoline gives tetrahedral $(3\text{-pic})_3CuX$ complexes (79ACH307). Preparation of Cobalt(II) halide and thiocyanate complexes with a series of mono-, di-, and tetramethylpyridines yields CoX_2L_2 and CoX_2L_4 , where L is a nonhindered pyridine, but fails when L is a 2,6-dimethylpyridine (81MI1). The stereochemistry of solid thiocyanatenickel(II) complexes with pyridine derivatives as ligands $[Ni(NCS)_2(q\text{-Rpy})_2]$ is pseudooctahedral (50) except with ortho-substituted pyridines $Ni(NCS)_2(2\text{-Rpy})_2$ (with $R = Me, Et$) (51), which proved to be square planar (Scheme 29).

When the central atom is Cu(II), all the complexes $M(NCS)_2L_2$ are octahedral irrespective of the ortho substitution of the pyridine ligand. But



SCHEME 29

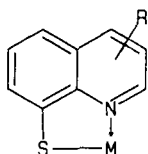
when the central atom is Co(II), the complex is tetrahedral with hindered pyridines (84MI1); these results indicate that the leading factor in the stabilization of Ni(II) complexes is the ligand interactions via the central atom (82CCR87).

Electron spin resonance (ESR) spectra of CdL_2X_2 (L = pyridine or substituted pyridine) show that axial distortions in complexes are affected by both steric and electronic effects (85MI4).

The effect of bulky ortho-substituted aza-aromatics on the stability of metal complexes depends mainly on the nature of the metal. In the case of complexation of Ag^+ with methylpyridines, a Brönsted-type equation correlates with complexation ΔH with the $\text{p}K_a$, indicating no direct steric effect to the approach of the Ag^+ ion (74BSF2793).

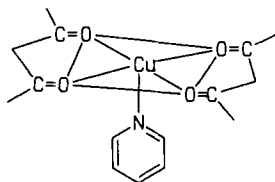
The stability of metal complexes (Zn, Cd, Pb, Ni, Ag, Bi) with alkyl-substituted 8-mercaptoquinolines (52) (Scheme 30) is lowered when a bulky substituent is introduced in position-2. For example, when nickel is the metal M, the $\log K_1$ of the stability constant and the corresponding substituent R in 52 are 9.5, H; 9.2–11.3, methyl in 4-, 6-, or 7-position; 8.1, methyl in 2-position; 3.9, *i*Pr in 2-position.

The complexation constant of methylmercury(II) with a series of pyridines decreases with increasing steric hindrance around the nitrogen atom in dichloromethane and nitromethane. However, this trend is reversed in methanol, with K increasing on going from pyridine to 2-methylpyridine and



52

SCHEME 30



SCHEME 31

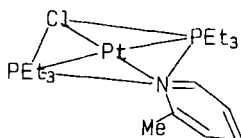
is leveling off with the more hindered 2,6-lutidine (85MI7). This behavior is similar to what was observed during quaternization of pyridines in methanol (81JCS(P2)409). The formation of Ag^+ and Ni^{2+} complexes with sterically hindered pyridines is very different; the formation of Ni^{2+} complexes is very restricted and independent of $\text{p}K_a$, whereas the K_1 complexation constant with Ag^+ follows $\text{p}K_a$ ($\alpha = 0.30$) (84MI2). Note that even if Ag^+ is very slightly sensitive to steric hindrance (83IC2531), the coordination constant of 2,6-DTBP is lower than expected from the Brönsted equation.

Copper (II) β -diketonates form 1:1 adducts with heterocyclic bases. With pyridine derivatives, there is a Brönsted plot between the log of the stability constant and the $\text{p}K_a$ (Scheme 31). The 2-methyl-substituted pyridines are on a parallel line and 2,6-dimethylpyridine falls below the line (78BCJ805). The picture is very similar to what is observed in quaternization of pyridines (83T4209).

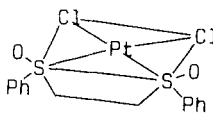
Complexes between lanthanide shift reagents (73MI1; 73CRV533) and heteroaromatic bases (71OMR575) are affected by steric effects. Data on 2,6-dimethylpyridine and 2,4,6-trimethylpyridine indicate a reduction of the Fermi contact mechanism, (72OMR557; 75CPB1905; 77CPB3177); calorimetric studies (81JCS(D)2434; 81MI2) and calculated nonbonded energies between methylpyridines and $\text{Eu}(\text{Fod})_3$ also show a reduced contact in the octahedral complex (83JCS(P2)1585). Steric hindrance due to benzo fusion (in the series pyridine, quinoline, acridine) results in a marked decrease in the binding constant to $\text{Eu}(\text{Fod})_3$ (80MI4). A detailed analysis of factors affecting the interaction of LSR with substituted pyridines shows evidence of a steric requirement of substituents originating in their bulkiness and conformations which may be modified by a buttressing effect (85TL4669).

Deuteration of all methyl groups in 2,4,6-trimethylpyridine causes a large (6%) isotope effect on the lanthanide-induced shift for the 3- and 5-hydrogen atoms, which is proposed to be steric in origin (76CC984).

In analytical chemistry 2,2'-bipyridyl and its derivatives have many applications they form bidentate chelating agents with metal ions, amongst them iron, ruthenium, copper, and platinum. However, a 6-substituent decreases the chelating ability of 2,2'-bipyridyl by a steric interaction, while 6,6'-disubstitution totally inhibits it.



SCHEME 32



SCHEME 33

Kinetic effects are observed in replacement of chloride ion in *trans*-(Pt(PEt₃)₂(*o*-tolyl)Cl) by various pyridines (Scheme 32). The reactivity of 2-methylpyridine is much lower (~ 100 times) than that of other 3-, 4-, or 5-methyl- or dimethylpyridines. This steric ortho-retarding effect is much greater than that found for other substrates of Pt(II), Pd(II), and Au(III) (74JCS(D)927).

Indeed, steric hindrance is absent when hindered amines are displaced from Au(am)Cl₃ (am = amine) in the presence of HCl (66IC1145).

Rate constants for chelate ring-opening in four-coordinated square-planar *d*⁸-platinum complexes [1,2-bis(phenylsulfinyl)ethane]dichloroplatinum(II) by a series of pyridines show from a negative deviation in a Brönsted plot ($\alpha = 0.53$) an estimated rate decrease of steric origin of ~ 200 for the 2-picoline (81IC71) (Scheme 33).

Kinetics of nucleophilic attack of pyridines on (Fe(π -hydrocarbon)(Co)₃)⁺ cations show a high Brönsted slope ($\alpha = 1.0$) and a rate decrease due to a steric effect of ~ 10 for a 2-methyl substituent and ~ 300 for a 2,6-dimethyl (81JCS(D)1162).

In displacement by chloride ion of heterocyclic nitrogen bases (am) from square-planar *trans*-(PtL(am)Cl₂), the reactivity is also reduced on -methyl substitution in the leaving pyridine (85JCS(D)27). This type of steric hindrance is absent when similar hindered amines are displaced from Au(am)Cl₃ (66IC1145). On the other hand, it is very common when the amine is an entering group and when a substituted ligand is coordinated *cis* to the leaving group (81IC71). So far, however, there is no case where a more bulky aza-aromatic leaving group is more easily displaced as in dequaternizations (76JOC2621; 84CSR47; 85H1765). This is an illustration of the difference in the reaction mechanisms for a metal and for an *sp*³-carbon atom. Quantitative results obtained from quaternization reactions may be transferred to reactivity of aza-aromatics with metals if the rate-determining step involving the coordination complex is identified correctly.

d. Acyl Halides and Related Compounds. Aza-aromatics are efficient nucleophilic catalysts of acylation reactions; among them, pyridine derivatives have been used for a long time (53JCS1406) and more recently "super nucleophiles" like dimethylaminopyridines (DMAP) have been proposed (78AG(E)569). α -Substitution, as in 2-methylpyridine, markedly

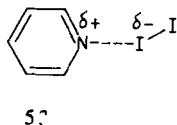
reduces the catalytic efficiency because of steric hindrance to attack of the nucleophilic ring nitrogen on the acyl carbon (61JCS4362), a typical kinetic ratio k_{py}/k_{2-mepy} being in the range 20–30 (82JOU2310; 83AJC1951). Generally pyridines and highly basic derivatives operate by a nucleophilic mechanism of catalysis (typical Brönsted α being 0.89, 0.74, and 0.60), but low-basicity pyridines ($pK_a < \sim 4$) operate by a general base mechanism, which may result in curved Hammett lines (69MI2).

Consequently, one may expect α -substituted pyridines to shift from nucleophilic to a general base catalysis with very bulky ortho substituents. With 2-amino- and 2-methylpyridine, however, the results seem consistent with nucleophilic catalysis throughout (83AJC1951).

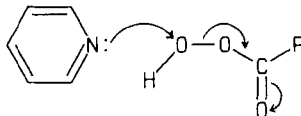
e. *Halogens and Interhalogens.* Halogens (X_2) and interhalogens (XX') give electron donor–acceptor (EDA) complexes (69MI3) with aza-aromatics. In the case of pyridine–iodine, an X-ray structure of the complex **53** exists (Scheme 34).

Substituents in the ortho position of the pyridine ring show a small steric effect. For example, pyridine and 2-methylpyridine have almost the same complexing ability toward I_2 (83JCP677) or BrI (78RRC1409), which may be explained by a long $N-X$ bond in the complex. A good correlation exists between the shift $\nu_{(I_2)}$ of the visible transition of iodine in complex formation with substituted pyridines versus the ν_{OH} band of methanol (related to pK_a). Deviations of ortho substituents below the regression line are correlated to S^0 parameters, except for ortho π -substituents such as 2-OPh, 2-vinyl, and 2-COPh, which are more active than expected, presumably because of a synergistic interaction of iodine with the π - and n -systems (83JCP677).

f. *Peracids.* Peracids react with aza-aromatics to form N-oxides. The reaction can be considered to be a nucleophilic substitution at oxygen (71MI1). In agreement with this proposed mechanism, a value of -2.35 , close to those of quaternizations, is observed in the reaction of 3- and 4-substituted pyridines with perbenzoic acid (47JA1962) (Scheme 35). However, since the R group in the peracid is not close to an ortho substituent of the pyridine ring, the reaction of perbenzoic acids with pyridine, methylpyridines, dimethylpyridines, and trimethylpyridines (61G613) appears less sensitive to steric effects



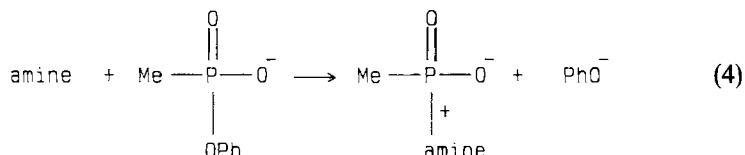
SCHEME 34



SCHEME 35

than quaternization. This is also observed with benzo-fused derivatives: Pyridine, quinoline, and isoquinoline have almost the same reactivity toward perbenzoic acid (66BS17).

g. Other Electrophiles. The reactions of phosphonic acid esters with amines have a rate-determining step compatible with Eq. (4).

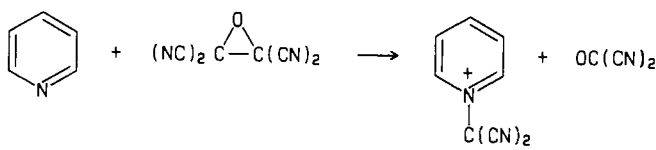


With pyridine derivatives the Brönsted and Hammett slopes are +0.35 and -2.1, respectively (70JA4675), again very similar to those obtained in quaternizations. However, owing to the bulk of the phosphorus reagent, steric strain with ortho-substituted pyridines now is larger than that found during quaternization. For example, pyridine reacts 20 times faster than 2-methylpyridine. The steric effects of 2-methyl- and 2-amino, estimated as $\log k$ from the Brönsted plot, are nearly twice that of the corresponding S° parameters (70JA4675).

Tetracyanoethylene oxide (TCNEO) reacts with nucleophiles (65JA3651; 69JOC2146). With aza-aromatics (68JA3830), the reaction affords stable *N*-dicyanomethylides, which further react as 1,3-dipoles in cycloaddition reactions (Scheme 36). Pardo *et al.* showed that the reactivity of aza-aromatics toward TCNEO increases with basicity and decreases with steric hindrance, and that only in a given number of cases does the reaction afford the corresponding dicyanomethylide (82JOC4409).

They proposed a plot which defines two regions where (under comparable conditions) the reaction does or does not occur (Fig. 7).

Although a quantitative measure of steric strain in the structures along the abscissa would make the picture more accurate, this is already an interesting scheme for predicting reactivity. It has been tested successfully with pyrimidines (86H3473).



SCHEME 36

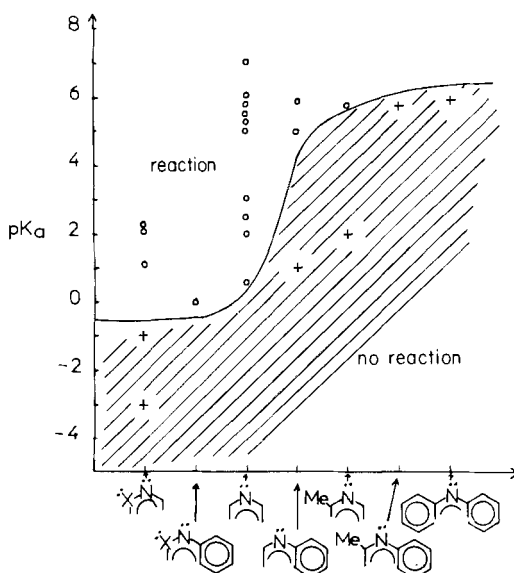


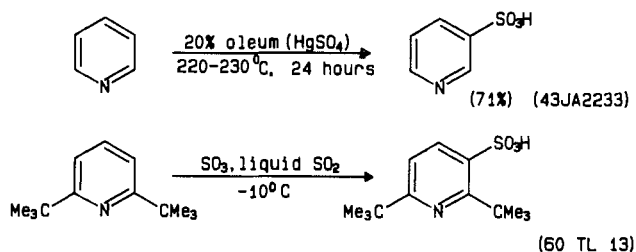
FIG. 7. Reactivity of aza-aromatics toward TCNEO: reaction occurs, ○; reaction fails, +.

C. π -REACTIVITY

1. Electrophilic Reactivity

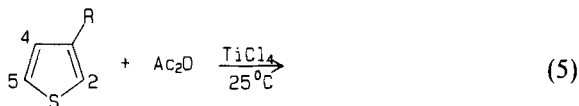
Few kinetic studies have been devoted to steric effects in reactions of electrophiles with heteroaromatics. Generally, regioselectivity data are reported (i.e., a ratio of isomers or partial rate factors). Five-membered heteroaromatics with one heteroatom are more reactive than benzene (the order being pyrrole > furan > selenophene > thiophene) and undergo preferential α - rather than β -electrophilic substitution. However, azines with pyridine-like nitrogens are deactivated, with an orientation meta to the nitrogen atom often existing in the reaction medium mostly as a protonated form. One example from sulfonation illustrates the drastic change in the reactivity of the pyridine ring when bulky ortho groups hinder the nitrogen atom (Scheme 37); in this case an appreciable amount of pyridine undergoes the reaction as the free base under rather mild conditions.

Bulky substituents show steric effects which change the usual selectivity, e.g., large 1-alkyl groups increase β -substitution in trifluoroacetylation (80JCR(S)42) and in the Vilsmeier formylation (70JCS(C)2572) of *N*-alkylpyrroles. With larger substituents like triphenylmethyl in position-1 of pyrrole, bromination, formylation, and trifluoroacetylation occur selectively



SCHEME 37

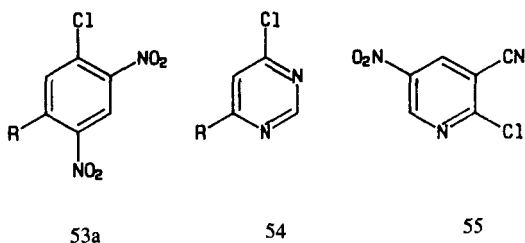
at the 3-position (83JCS(P1)93). The magnitude of the steric ratio defined as the ratio of partial rate factors $2f/5f$ is 17.8 for 3-methylthiophene and 3-*t*-butylthiophene in the acylation with Ac_2O [Eq. (5)]. However, acylation of 2-phenyl-5-alkylthiophenes (73T413) shows that the steric $\text{Me}/t\text{-Bu}$ ratio depends on the nature of the acylating agent and the solvent. The ratio of f/mf for the pair toluene/*t*-butylbenzene under reaction conditions of Eq. (5) is 44,200 (71TL611). These relative values agree with differences in geometry of five- and six-membered rings (71T4667).



A comparable steric $\text{Me}/t\text{-Bu}$ ratio of 40 is observed in the *N*-methylation of five-membered rings like thiazole, indicating a greater sensitivity to steric effects when the reaction occurs in the plane of the ring (72TL3857).

2. Nucleophilic Reactivity

Nucleophilic heteroaromatic substitutions (64AHC(3)285) are activated by pyridine-like nitrogens and by electron-withdrawing groups, the order of activating ability being $\text{NO}_2 > \text{N (heterocyclic)} > \text{CF}_3 > \text{CN} > \text{X} > \text{H}$ (68M11). Consequently, steric effects in these reactions will come not only from primary steric effects (PSE), which involve a direct interaction between a substituent on the ring and the incoming nucleophile or leaving group, but also from secondary steric effect (SSE), where there is no direct interaction with the incoming nucleophile. The reason is that heteroaromatics undergoing $\text{S}_\text{N}\text{Ar}$ reactions are activated by electron-withdrawing substituents, like nitro, which are very prone to conformational changes induced by an adjacent group, resulting in a modification of reactivity due to steric inhibition of resonance (SIR). SSE can be easily estimated when the activating group and the ortho substituent are not adjacent to the leaving group by comparing



SCHEME 39

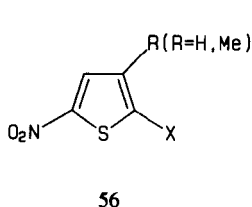
the reactivity of the aza-aromatic to that of the equivalent benzene derivative, e.g., the rate decrease on going from $R = \text{methyl}$ to $t\text{-butyl}$ in the reaction of pyridine with **53a** (~ 16) can be attributed mainly to SIR because the similar change in **54**, due to inductive effect, is only 2.5 (57JCS600) (Scheme 39).

An SSE is also observed in the reaction of **55** with aniline. When a methyl group is introduced in the 6-position and when a second methyl is introduced in the 4-position, the rate decreases are, respectively, 4 and 81 (62JCS1975).

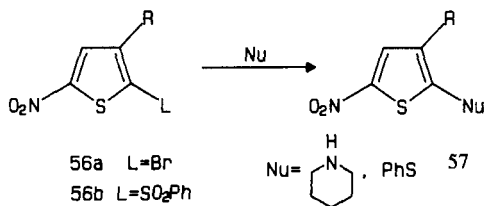
Quantitative studies of PSE and SSE have been carried out systematically by the Spinelli and by the Gronowitz groups in the thiophene series. In the pyridine dehalogenation of thiophene derivatives **56** (Scheme 40), the presence of a methyl ortho to the leaving group does not cause a PSE (75JCS(P2)816), in contrast to what is observed in the benzene series (56RTC1137; 57JCS600; 65JOC3365), because of geometrical differences in six- and five-membered rings (74JCS(P2)1632). In the thiophene series, only with a leaving group of high steric requirement like phenylsulfonyl was a small PSE observed.

A better evaluation for the PSE was obtained from the reaction of thiophenes **56a** and **56b**, where R is a series of alkyl groups of different size (Scheme 41). Going from $R = \text{H}$ to methyl results in a rate decrease of ~ 4 , which is typical of the electronic effect of methyl in $S_N\text{Ar}$ reactions with no PSE.

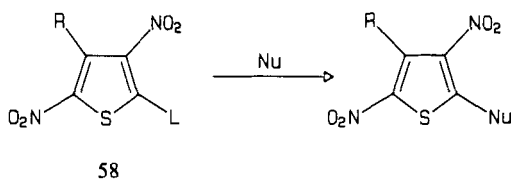
Changing the methyl to a linear alkyl group ($R = \text{Me, Et, } n\text{Pr, } n\text{Hex}$) brings almost no variation in the rate decrease ($k_H/k_R = 4\text{--}5$). In contrast, varying the alkyl group R in the α -position (methyl, ethyl, isopropyl, t -butyl) results in a strong rate decrease: Respectively, $k_H/k_R = 4, 5, 15, 110$ (77CS175). This



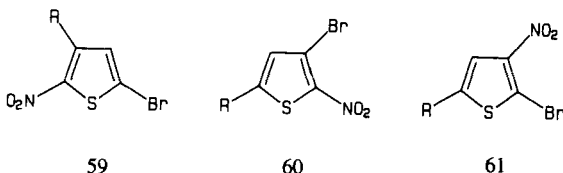
SCHEME 40



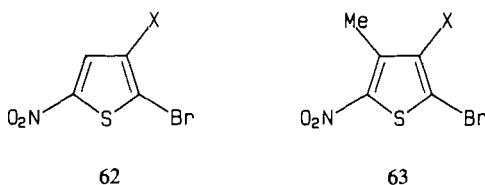
SCHEME 41



SCHEME 42



SCHEME 43



X=CONH₂ and other groups

SCHEME 44

behavior is in full agreement with what was observed in the quaternization of thiazoles (76JA1260; 79BSF(2)484) and of pyridines (78AP650). The PSE of an *o*-alkyl group is thus more important if the group is substituted in an α -position than if it is linear or substituted in a β - or a more remote position. Complementary results show no SSE in reaction of thiophene **58** (where L = Br and R = methyl) with nucleophiles (75JCS(P2)1388) (Scheme 42).

When R = isopropyl, and the nucleophiles are aniline, piperidine, and *N*-methylaniline, the ratio k_H/k_R is the same (~ 7) for L = Br, but it is 60, 96, and 110, respectively, for L = SO₂Ph (78CS130). Here again the SSE is much larger in the similar benzene derivatives (57JCS600; 72JCS(P2)1807). More puzzling is the rate acceleration caused by a methyl (compared to H) in structures **59**, **60**, and **61** (Scheme 43), where a rate decrease by an inductive effect (in **59**, **60**, and **61**) and by SIR (in **60**) was expected (82JCS(P2)625).

Interestingly, the fact that CONH₂ deviates strongly from a correlation between the logarithmic kinetic constants for the piperidino-substitution of **62** versus that of **63** (Scheme 44) has been interpreted in terms of steric

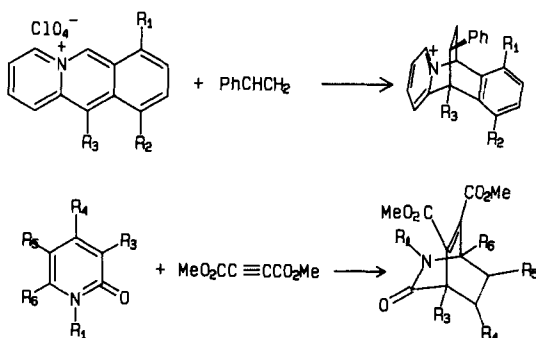
interactions and restricted rotation of the carboxamide and verified by DNMR spectroscopy (85JCS(P2)523).

D. MISCELLANEOUS

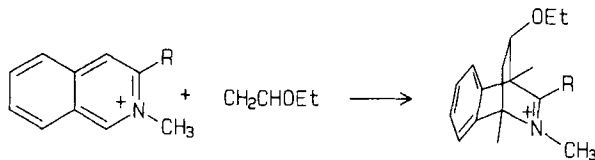
Owing to the variety of heteroatoms and to the diversity of structural situations, heterocycles undergo a vast number of reactions. A complete coverage of all the cases where steric effects occur is not the purpose of this subsection; we will report selected examples of miscellaneous reactions where steric effects have been quantitatively identified.

Steric enhancement of reaction rate has been reported in cycloaddition of styrene to acridinium ion (74JOC1172) and of 2(1*H*)-pyridone to dimethyl butynedioate (79CC501) when methyl groups are either ortho or peri (Scheme 45).

A similar behavior is observed in the cycloaddition reaction of isoquinolinium iodide with ethyl vinyl ether (Scheme 46). Steric strain of adjacent substituents is released in the TS resulting in an additional rate increase for $R = t\text{-Bu}$, as evidenced by an upward deviation in the Hammett plot (77JA2588).



SCHEME 45



SCHEME 46

TABLE V
S° PARAMETERS FOR THE ORTHO STERIC EFFECT

Entry	Substituent	S°	Reference
1	H	0	(80JCS(P2)1350)
2	Me	−0.73 ^a	
3	Et	−1.08 ^a	
4	iPr	−1.44 ^a	
5	<i>t</i> -Bu	−3.94 ^a	
6	<i>n</i> Pr	−1.20	(76JMC483)
7	<i>i</i> Bu	−1.29	
8	CH ₂ Ph	−1.16 ^a	(80JCS(P2)1350)
9	CH ₂ OH	−0.67 ^a	
10	CH ₂ CH ₂ OH	−0.86 ^a	
11	Cl	−0.54 ^a	
12	Br	−0.82 ^a	
13	CN	−0.89 ^a	
14	NH ₂	−0.93 ^a	
15	NHAC	−1.93 ^a	
16	NMe ₂	−2.32	
17	OMe	−1.28	
18	OEt	−1.36	
19	CH=CH ₂	−1.48	
20	CHO	−2.36	
21	COMe	−2.28	
22	CO ₂ Me	−1.04	
23	CO ₂ Et	−1.25	
24	Ph	−1.82	
25	2-tolyl	−0.77	
26	Mesityl	−0.23	
27	4-Methoxyphenyl	−1.82	
28	4-Nitrophenyl	−2.18	
29	2-Thienyl	−2.46	
30	2-Thienyl-3-methyl	−1.75	
31	1-Naphthyl	−0.75	
32	2-Pyridyl	−2.35	
33	2,3-Benzo	−0.85	(83T4209)
34	2,3-Dimethyl	−0.92 ^a	(83T4209; 84JA143)
35	2-Methyl-3-ethyl	−0.8	(84JA143)
36	2-Methyl-3- <i>i</i> Pr	−0.86	
37	2-Methyl-3- <i>t</i> Bu	−1.11	
38	2-Ethyl-3-methyl	−1.12	(84JA143)
39	2- <i>i</i> Pr-3-methyl	−3.00	
40	2,3-Cyclopentano	−0.08	
41	2,3-Cyclohexano	−0.53	
42	2,3-Cycloheptano	−1.05	
43	2,6-Dimethyl	−1.98 ^a	(83T4209; 84JA143)
44	2,6-Diethyl	−3.01	(84JA143)
45	2,3,6-Trimethyl	−2.3 ^a	(83T4209; 84JA143)
46	2,3,5,6-Tetramethyl	−2.85 ^a	

^a Mean value from two or several independent studies.

E. STERIC PARAMETERS FROM HETEROCYCLIC MODELS

The ortho-steric parameters given in this paragraph are derived from N-methylation of pyridines. The basic set was calculated by the general equation

$$S^0 = \log(k/k_H) - (\alpha pK_a + c)$$

where k is the quaternization rate constant of the ortho-substituted pyridine; α and c are the Brönsted parameters with non-ortho pyridines, all in the same solvent (80JCS(P2)1350). When several S^0 values were available, from studies in different solvents, a mean S^0 value was taken (Table V, entries 1–5, 7–32). Additional values reported later in the literature have been added if calculated according to the same procedure (entries 31–46). Further additional values, for which a Brönsted slope was not available, were calculated referring to the substituted pyridine having almost the same pK_a , i.e., for entries 6 and 7.

$$S^0_R = S^0_{Me} + \log(k_R/k_{Me})$$

III. Intramolecular Steric Effects: Dynamic Stereochemistry

The conformational analysis of substituted heteroaromatic systems will be discussed. The material is organized with respect to the steric properties of the substituents, rather than the type of heteroaromatic systems. The number of combinations in regard to ring size, the type and the number of heteroatoms, and their relative position give a nearly unlimited variety of steric and electronic properties of the heterocyclic ring. From a steric point of view, however, the ring system may usually be regarded as an essentially rigid planar framework, with which the attached substituents interact sterically and electronically.

The substituents, on the other hand, are more diverse as to their interactions with their surroundings, and may be divided into classes with respect to their local symmetry. This is related to the hybridization of the atom by which the substituent is attached to the ring: (1) substituents with local c_∞ axes, such as halogen, cyano, etc. (sp -hybridized bridgehead atom); (2) planar substituents, such as heteroaromatic rings, the formyl, and others (sp^2 -hybridized bridgehead atom); (3) polyhedral substituents, such as alkyl groups (sp^3 -hybridized bridgehead atom).

Nonbonding interactions play a major role in determining the three-dimensional structure of a molecule. Such interactions are composed of repulsive and attractive contributions, such as van der Waals repulsion, London dispersion forces, coulombic interactions, and delocalizations of electrons due to the through-space interactions between atomic orbitals.



SCHEME 47

When conjugation is possible between the heterocyclic ring and the substituent, preference for maintaining a planar arrangement for maximum conjugation is balanced against the nonbonded interactions.

Thus, intramolecular steric effects are of primary importance in determining the conformation of alkyl and aryl substituents attached to heterocyclic frameworks. The dynamic processes associated with these conformational states are also strongly dependent on the steric modifications between ground state and transition state. It can thus be inferred that a quantitative approach of steric effects can be obtained through these data.

Since we are dealing with heteroaromatics, the dynamic stereochemistry will essentially concern the study of the processes associated with sp^2-sp^3 -bond and sp^2-sp^2 -bond systems, with the sp^2 -atom X being a carbon or a nitrogen atom belonging to the heteroaromatic system. (Scheme 47).

A. PHYSICAL AND THEORETICAL METHODS

The structure of a molecule may be studied in the gas phase, in solution or liquid state, or in the solid or crystalline state, and different techniques are applied. Furthermore, the various methods give different and sometimes complementary information on structure, conformation, and dynamics.

X-Ray diffraction (72PMH(5)1) gives static structural information of the symmetry of the conformation in addition to details such as bond lengths and bond angles, and even the intermolecular disposition of the molecules. A fundamental limitation of the X-ray method is that it is only applicable to the crystalline state and that the geometrical results obtained therefrom may be distorted by specific interactions in the crystal lattice. Nevertheless, the huge amount of X-ray data on molecular structure, easily available through the Cambridge Crystallographic Data Centre, also constitutes an invaluable source for conformational analysis. A compilation of the X-ray data for heterocyclic compounds is available (72PMH(5)1).

Microwave spectra (74PMH(6)5) provide a rich source of detailed molecular structures in the gas phase. For molecules with more than four atoms the isotopic replacement technique must be used in order to obtain a complete structure. Not only the ground-state conformation but also rotational barriers

may be obtained from microwave spectra, provided that the molecule contains only one or few rotating groups.

Electron diffraction (71PMH(3)27) is predominantly a gas-phase method. By this method, mixtures of conformations can be detected, but rotational barriers can only be estimated in special cases. Microwave spectroscopy and electron diffraction have given many valuable structural determinations in the gas phase, especially for the parent heterocycles and simple derivatives.

Infrared (IR) and Raman spectroscopy (71PMH(4)265) are of limited value in the conformational analysis of more complex molecules, since it is usually impossible to identify the bands, and to distinguish between fundamentals and overtones and combination tones.

Nuclear magnetic resonance (NMR) spectroscopy (71PMH(4)121) is by far the most useful spectroscopic method to study conformations and barriers to conformational interconversions, not only in solution but also in the gas phase and in the solid state. The use of multinuclear NMR and two-dimensional techniques in addition to more conventional methods offers an enormously rich arsenal of tools to attack conformational problems. Variable-temperature NMR (DNMR) may be used to investigate processes with free energy barriers in the range 20–100 kJ mol⁻¹ (75MI1; 85MI2; 80MI1; 82MI2). Lower barriers may be determined in special cases by other NMR methods, such as ¹³C-spin lattice relaxation measurements and coupling constant measurements (80ACR400). By the DNMR technique, two or more conformers are detected at low temperature, provided that their populations exceed ~1%. When more than two conformers are observed, careful band-shape analysis of spectra at different temperatures provides evidence for preferred pathways for the conformational interconversion. Band-shape analysis of the broadened NMR spectra gives the rate constant and the free energy of activation (ΔG^\ddagger), the energy quantity obtainable by DNMR that is least sensitive to systematic errors. The temperature dependence of the rate constants allows the evaluation of enthalpy and entropy components, in principle the most informative parameters. Unfortunately, systematic errors in ΔH^\ddagger and ΔS^\ddagger are often too large to permit their use in precise discussions.

Circular dichroism (CD) and optical rotatory dispersion (ORD) spectra (71PMH(3)397) are very sensitive to the spatial disposition of the atoms in a molecule, and conformational changes may yield rather dramatic changes in the appearance of a CD or ORD spectrum of a chiral molecule. The analysis of the temperature dependence of the CD spectrum may give information on populations and free energy differences. Except for nucleosides, the use of the chiroptical method in conformational analysis is rather limited, which may be accounted for by the complexity of the theory for optical activity.

When possible, the resolution of enantiomers due to restricted rotation allows the study of racemization rates by polarimetry. This time-honored

method, which gives exceptionally high precision in the various activation parameters, will be reinforced by the extraordinary developments of chromatographic resolution of enantiomers on chiral phases (85MI3; 86MI1; 86MI3).

Theoretical calculation of conformational energies and of barriers separating molecular conformations requires a theoretical model that accurately represents all the nonbonded and bonded contributions to the potential energy of the system. In principle, this could be done, provided that exact solutions to the Schrödinger equation were available. The application of *ab initio* molecular orbital (MO) methods to the simplest of heteroaromatic parent systems and to a few derivatives is now possible, but at the expense of large amounts of computer time (77JCS(P2)1601; 78JA3981; 79JA311). Calculations on the *ab initio* level, will doubtlessly gain increased importance in solving chemical problems in the future.

Semiempirical molecular orbital computations have been used in numerous studies to establish various properties of heteroaromatics, such as conformations and rotational barriers. The value of such calculations is more difficult to estimate; sometimes good agreement with experiment is obtained, sometimes not, making their predictational power questionable. The benefits of semiempirical MO computations are, of course, that large systems may be studied at much lower expense in terms of computer time. Thus, MINDO/3 calculations, which also take solvent effects into account, have been used to rationalize the syn-anti preference in the 2-formyl derivatives of furan, pyrrole, and thiophene (81JHC1055).

An entirely different approach, based upon classical mechanics, is the molecular mechanics or empirical force field method (82MI5; 83AG(E)1; 86MI2). It is assumed that the steric energy (E_s) of a molecule can be expressed as a sum of energy contributions [Eq. (6)], where each term is obtained from a simple potential function, such as the one given by Hooke's law.

$$E_s = E_{\text{stretch}} + E_{\text{bend}} + E_{\text{torsion}} + E_{\text{VDW}} + \text{Cross terms} \quad (6)$$

The potential functions are parameterized to give a realistic force-field, and the total steric energy of a molecule is found by minimization with respect to all internal degrees of freedom. Any desired local minimum on the potential energy surface, i.e., all stable conformers, can be located by the variation of the input structure. One may even construct a complete conformational map, by varying the relevant torsional angles and calculating the energies, to trace transition states and to study pathways leading from one conformer to another (85ACR80). Molecular mechanics calculations are performed on small to moderate size computers in comparatively short time.

Today's force fields give results that are competitive to experimental results for hydrocarbons and certain simple hydrocarbon derivatives, but application

to heteroaromatics have hitherto been hampered by the lack of adequate force-field parameters. However, in the new version of the best established force field (MM2) (1985 force field) by Allinger *et al.*, parameters for heteroaromatics have been incorporated. Thus, pyridine, pyrrole, furan, thiophene, and many compounds containing two or more heteroatoms in a five- or six-membered ring can now be dealt within the program.

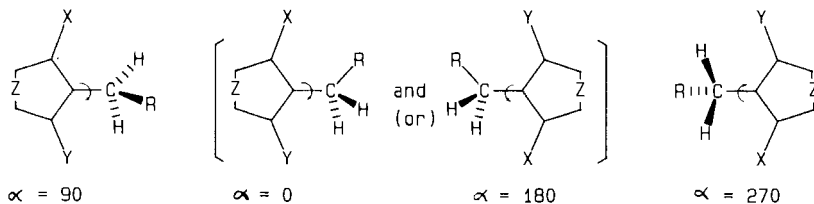
B. HINDERED ROTATION AND CONFORMATIONAL STATES OF SUBSTITUENTS ATTACHED THROUGH AN sp^3 -ATOM

Barriers to rotation and conformational states around sp^2 – sp^3 play an important role in the determination of the steric requirement of a substituent. These barriers are predominantly composed by the difference in through-space nonbonding interactions in ground and transition states. They are typically free from electronic contributions, in contrast to the quantitative approach of steric effects, which proceeds through reaction rates or $(\sigma + \pi)$ -barriers to rotation, in which the steric part is only a perturbation of the energetic content.

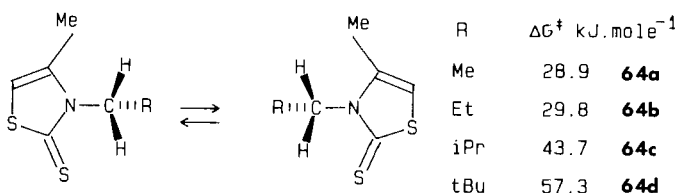
The material of this section will be arranged in the following way. First, we treat the conformational states and barriers to rotation of substituents attached by a primary carbon atom. Second, we consider the case of a secondary carbon bridge atom. And third, we treat the case of interactions between these groups.

1. Substituents Attached by a Primary Carbon Atom

A single primary group attached to a planar framework is expected to have a "perpendicular" energy minimum, where the angle α and the barrier to rotation depend on the relative sizes of the flanking groups X and Y and the size of the rotating R group. The two isomeric transition states between the two enantiomeric ground states are those in which the rotating R group passes in front of the X or the Y flanking substituents (Scheme 48).



SCHEME 48



SCHEME 49

The treatment of quantitative data (ΔG^\ddagger , $\log k$, etc.) to obtain information on the steric requirements of substituents (X, Y, R) can be performed in two different ways. (1) If X and Y are kept constant, the barrier to rotation of a CH_2R group measures the size of the group R. This method has been used in derivatives of benzene (68JA5502; 75ACS(B)300). (2) If R is kept constant, the height of the barrier is determined by the sizes of X and Y. Both groups hinder the rotation, but R will preferentially pass the smaller one and thus a steric scale can be obtained (74JA3190).

The resulting barriers give an insight into the geometric requirement of the framework for a given trio X, Y, and R. The barriers to rotation about the $\text{N}-\text{CH}_2$ bond have been measured by DNMR in a series of 3- RCH_2 -4-Me- Δ^4 -thiazoline-2-thiones (**64a-d**) (75TL1985; 80OMR120) (Scheme 49).

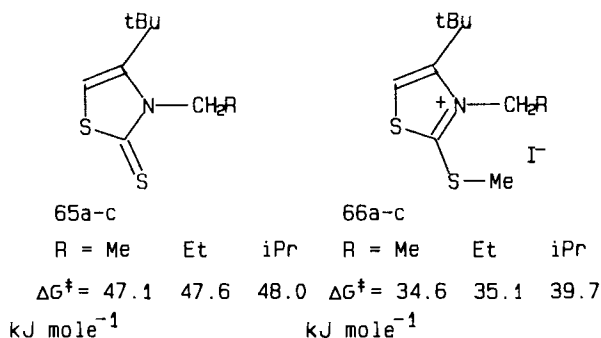
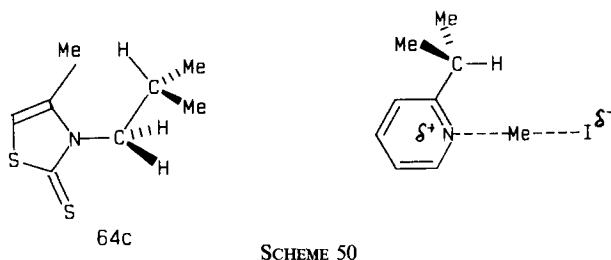
In these compounds, the transition state corresponds to the passage of the R group in front of the 4-methyl substituent (Scheme 49) and thus the barriers give a direct measurement of the steric interaction between the alkyl group R and methyl. The relative size of the isopropyl group compared to other alkyls is found to be larger in this process than that determined by a quaternization reaction of 2-alkylpyridines or 2-alkylthiazoles. This is easily accounted for by considering the difference in backbone contributions. In 2-isopropylthiazole or -pyridine, the isopropyl group can rotate its bulky face away from the incoming methyl group, without appreciable energy penalty arising from backbone contribution; in 3-isobutylthiazolinethione **64c**, rotation of the isopropyl group to minimize the steric interaction with the 4-methyl group will cost the eclipsing energy with the CH_2 fragment (Scheme 50).

This is a clear example of the importance of a conformational effect in determining the relative size of noncentro symmetric substituents.

Methylation at sulfur decreases strongly the barriers to rotation, the methylthio group being less bulky than the thione group (80OMR120).

A limit to the use of these steric barriers for the determination of the relative size of alkyl groups was pointed out in the study of the rotational barriers in 4-*t*-Buthiazoline-2-thiones **65a-c** and in **66a-c** (Scheme 51).

In compounds **65a-c**, the transition states correspond to the passage of the



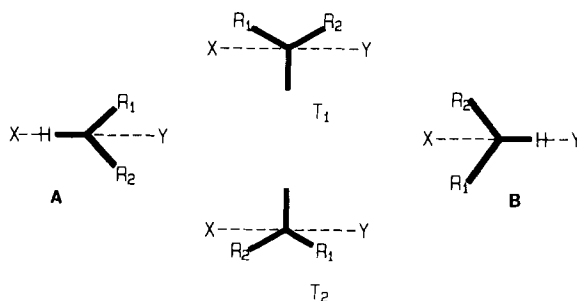
SCHEME 51

R group in front of the thiocarbonyl sulfur atom. The experimental barriers were constant in the series $R = \text{Me}, \text{Et}, i\text{Pr}$. This abnormal behavior was accounted for by considering the increase in strain in the ground state as was shown by molecular mechanics calculations (80OMR166). The barrier to rotation of the neopentyl group was determined in anhydro-2-methylthio-3-neopentyl-4-hydroxy-5-phenylthiazoline hydroxide ($\Delta G^\ddagger = 45 \text{ kJ mol}^{-1}$) (86ACS(B)751). Many other heteroaromatic series are suitable for such studies.

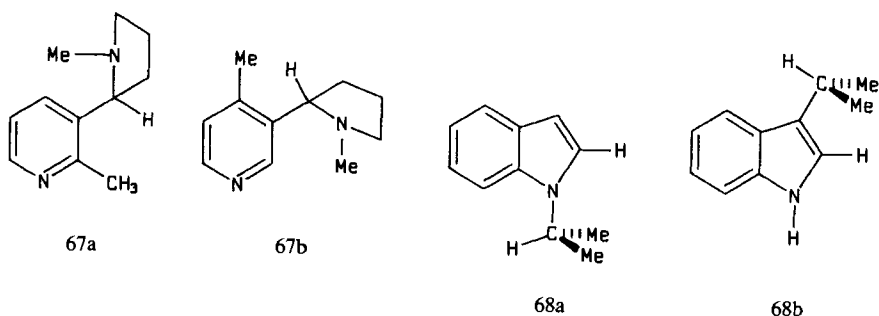
2. Substituents Attached by a Secondary Carbon Atom

The conformational states and barriers to rotation of a CHR_1R_2 group attached to a planar framework have provided an unprecedented source for the detailed analysis of the steric requirement of flanking substituents X and Y (Scheme 52) in benzenes (68CJC2187; 68TL5939; 70AG(E)806; 71CB228; 74CJC849; 77CB3258) and heterocycles (71TL1861; 76JA2847).

When the two groups X and Y present a large difference in steric requirements, the equilibrium B/A is totally shifted toward the conformation in which the bulky R_1 and R_2 groups are directed away from the larger X or Y.



SCHEME 52



SCHEME 53

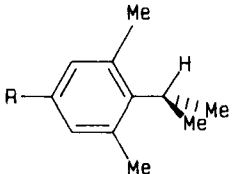
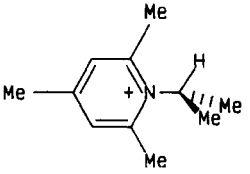
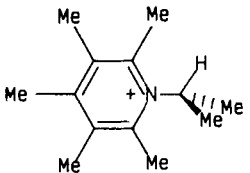
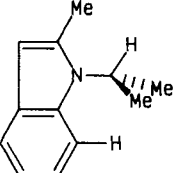
This is the case in 2-methyl- and 4-methylnicotine derivatives **67a** and **67b**, in which the relative conformation of the pyrrolidine and the pyridine rings depends upon substituents in the 2- or 4-position (81JOC3040), as well as in 1-isopropyl- or 3-isopropylindoles **68a** and **68b** (84ACS(B)491) (Scheme 53). In such cases the barriers to rotation are not accessible by DNMR.

When $R_1 = R_2$, such as for *i*Pr or cyclohexyl groups, the substituent assumes one of the "bisected" isomeric conformations, A or B (Scheme 52), which are sometimes better represented as enantiomeric pairs of slightly twisted conformations separated by a low barrier. The position of the equilibrium between these conformations depends on the relative effective size and shape of the flanking substituents X and Y. More precisely, it is a quantitative indication of the differences in through-space interactions between $[2(R/X) + (H/Y)]$ in A and $[2(R/Y) + (H/X)]$ in B for a given geometry.

When the barrier to rotation is high enough to allow the freezing of the exchange between the two conformations, the equilibrium constant is easily determined by low-temperature NMR spectra by simple integration.

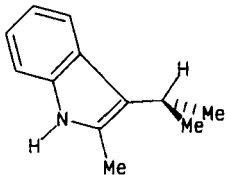
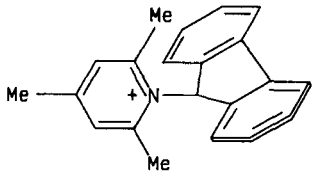
TABLE VI
SELECTED EXAMPLES OF BARRIERS TO ROTATION IN ISOPROPYL HETEROCYCLES

Compound	X	Y	% A	Solvent	ΔG^\ddagger (kJ mol ⁻¹) (T, °C)	Reference
	C=S	Me	15	CDCl ₃	63.1(302)	(71TL1861) (76JA2847)
	C=S	Me	30	C ₃ D ₆ O	59.0(298)	(76JA2847) (85JCS(P2)273)
	C=S	Me	15	C ₃ D ₆ O	50.4(256)	(85JCS(P2)273)
	C=S	Me	26	C ₃ D ₆ O	44.3(220)	(85JCS(P2)273)
	Me	Me	51	CHFC1 ₂	49.7(210)	(83T4209)

	Me	Me	50	C_3D_6O	53.7	R = Me (71CB228) R = MeO (83TL2259)
	Me	Me	50	$CHCl_2$	66.5(298)	(83T4209)
	Me	Me	50	$CHCl_2$	58.1(273)	(83T4209)
	H peri	Me	86	$(CD_3)_2O$	46.2(190)	(84ACS(B)491)

(continues)

TABLE VI (Continued)

Compound	X	Y	% A	Solvent	ΔG^\ddagger (kJ mol ⁻¹) (T, °C)	Reference
	Me	H peri		(CD ₃) ₂ O	< 35	(84ACS(B)491)
					> 142	(84JST(114)363)

The energy content of the transition states T_1 and T_2 (Scheme 52) depends on the steric interactions of the R groups with both X and Y, since the two R groups are situated on the same side of the plane defined by the heterocycle. The barriers will be strongly dependent on the geometrical relationship within the quartet X, Y, R_1 , and R_2 . When X and Y = H, one expects a low barrier to rotation ($\sim 8 \text{ kJ mol}^{-1}$) and a preferred conformation such as A or B by analogy, to the behavior of an isopropyl group in isopropylbenzene (77JMR167).

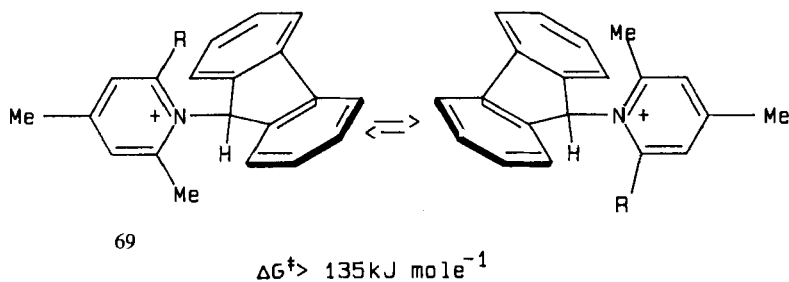
Since the first study of 4-Me-3-*i*Pr- Δ^4 -thiazoline-2-thione (71TL1861), many other heterocycles with an isopropyl group have been examined and some selected examples in which X and Y are different from hydrogen are given in Table VI. The experimental barriers to rotation cover a wide range of energy depending on the spatial relationship between the rotating group and the flanking substituents. As expected, the length of the linking bond is of primary importance as well as the geometry of the heterocycle (83T4209; 84ACS(B)491; 85JCS(P2)273).

Isolable rotamers of the *N*-9-fluorenylpyridinium salts **69** were obtained, owing to restricted rotation around the $C(sp^3)$ — $N(sp^2)$ single bond (84JST(114)363) (Scheme 54).

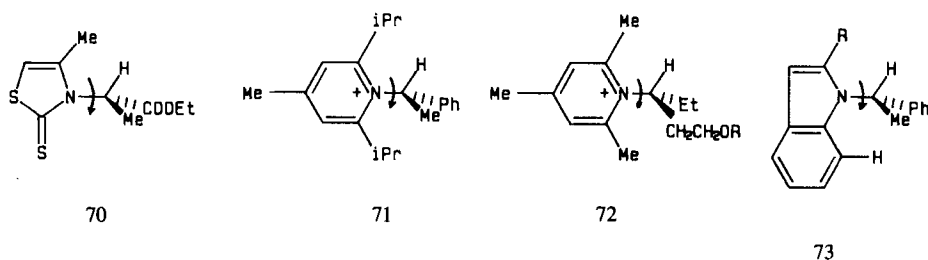
After isolation, the isomerization proceeds with a measurable rate, but dealkylation leading to the pyridine competes with isomerization and it is still a matter of speculation whether the observed isomerization occurs with or without (rotation) bond breaking. Examples of analogous hindered rotations in the benzene series have been reviewed (84ACR154).

Various heterocyclic compounds in which $R_1 \neq R_2$ have been studied and the barriers to rotation determined on racemates or optically active forms of **70** (76TH1; 80CJC2212), **71** (83OMR587), **72** (80TL1553; 84T2547; 85ZN(B)1555), and **73** (85TH1; 86ACS(B)625) (Scheme 55).

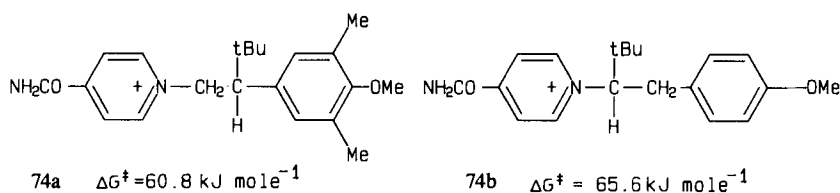
The general features for conformational structure and steric effects on the barriers are maintained. Fairly high barriers to rotation were determined in isomeric pyridinium salts **74a** and **74b**, in which X and Y are hydrogens



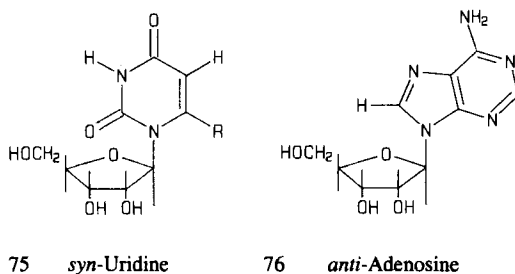
SCHEME 54



SCHEME 55



SCHEME 56



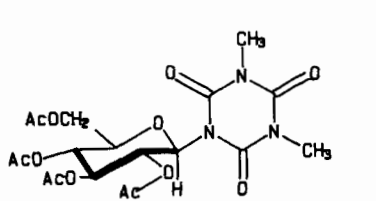
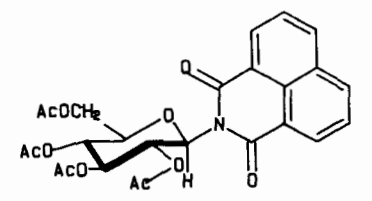
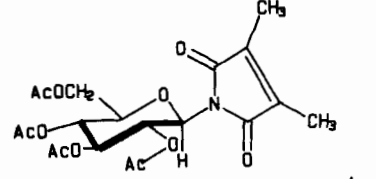
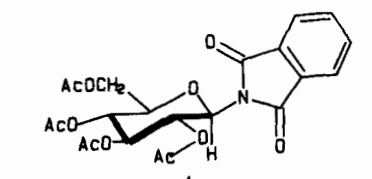
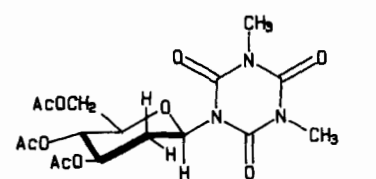
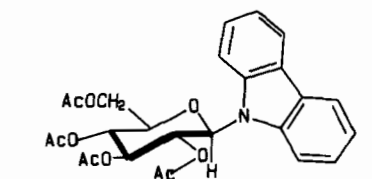
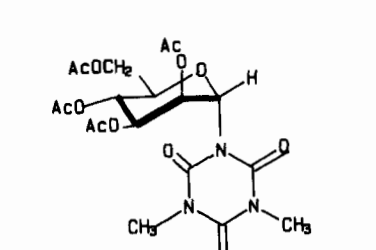
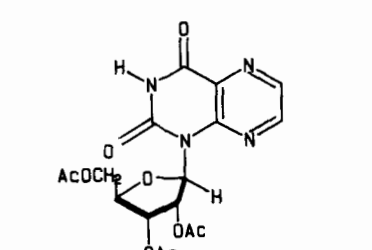
SCHEME 57

(Scheme 56). The effect of the bond length is clearly evident when comparing the barrier in **74a** and **74b** (74RTC61).

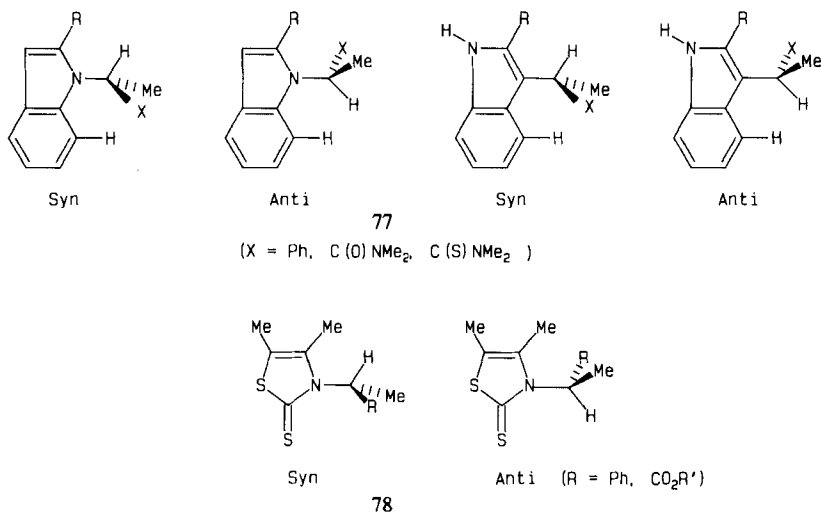
Barriers to rotation have been determined by DNMR for various heterocyclic systems by Jochims and co-workers. (78CB1693; 78CB2010; 78CB2745) Some selected examples are given in Table VII; they clearly show the importance of substitution on the sugar residue as well as the geometry of the heterocycle on the resulting barriers.

For chiral molecules, circular dichroism is a powerful method to analyze conformations. This method has been applied to pyrimidine and purine nucleosides and nucleotides, which may exist in *syn* and *anti* conformations A and B with respect to the glycoside (e.g., **75** and **76**, Scheme 57).

TABLE VII
SELECTED EXAMPLES OF BARRIERS TO ROTATION IN SUGAR DERIVATIVES

 <p>$\Delta G^\ddagger = 69.2 \text{ kJ mole}^{-1}$</p>	 <p>$\Delta G^\ddagger = 69.2 \text{ kJ mole}^{-1}$</p>
 <p>$\Delta G^\ddagger = 53.4 \text{ kJ mole}^{-1}$</p>	 <p>$\Delta G^\ddagger = 55.5 \text{ kJ mole}^{-1}$</p>
 <p>$\Delta G^\ddagger = 48.8 \text{ kJ mole}^{-1}$</p>	 <p>$\Delta G^\ddagger = 61.0 \text{ kJ mole}^{-1}$</p>
 <p>$\Delta G^\ddagger = 41.8 \text{ kJ mole}^{-1}$</p>	 <p>$\Delta G^\ddagger = 51.5 \text{ kJ mole}^{-1}$</p>

The syn and anti conformations of pyrimidine ribonucleosides have an opposite sign for certain transitions (e.g., the B_{2u} transition) (67B843; 69JA831; 71JA(93)1600; 72JCP2736; 72MI3). Such relations are empirical correlations, since the molecular structures are too complicated to allow theoretical calculations of the rotational strengths. A combination of DNMR, CD spectroscopy, and molecular mechanics calculations has been applied to derivatives of indole **77** and thiazoline-2-thione **78** substituted by chiral rotors (Scheme 58). In these molecules the rotor adopts one of the bisected



SCHEME 58

conformations (syn, anti, A, or B), with the larger groups of the rotor on either side of the planar sp^2 framework, as depicted in Scheme 58 (86ACS(B)625; 87JA492; 87ACS(B)261).

Molecular mechanics calculations and temperature-dependent CD spectra may reveal details of the conformational map not attainable by DNMR. Thus, double minima within each of the anti and syn forms were inferred from molecular mechanics calculations and were also supported by the temperature dependence of the CD spectra. Rotational strength calculations for the stable conformations predicted by the molecular mechanics calculations (or for any other arrangement) are in fair agreement with respect to both the sign and the dissymmetry factor for many of the studied compounds and may also allow for tentative assignments of absolute configuration in cases where this is not known (87JA492).

These studies reveal limitations in all the techniques, but also that the combined results from all the methods provide a conformational picture that would not have been obtained by the use of any one of the methods alone.

3. Steric Interplay of Substituents Attached to a Heterocyclic Framework

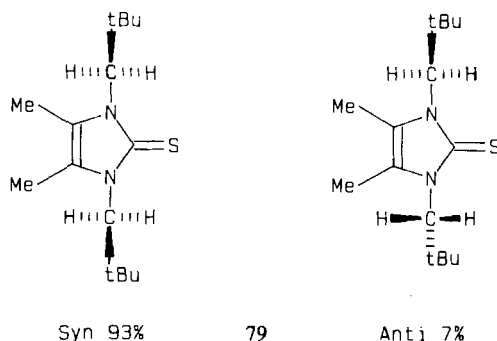
When several sp^3 -hybridized substituents are attached to a planar framework, their mutual interactions lead to conformational states and interconversion pathways that complicate the simple pictures given in

Sections III,B,1 and 2. The main feature is that one substituent cannot be treated independently from the others.

The topic of this section has been reviewed (85ACR80) for planar structures in general. We shall illustrate our discussion with heterocyclic systems which provide clear-cut cases of steric interplay.

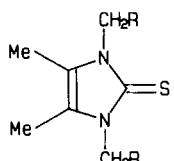
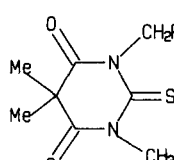
Vicinal primary alkyl groups attached to a planar framework are arranged alternatively above and below the plane so as to minimize repulsion (85ACR80). In less crowded molecules, however, the conformation is sometimes determined by attractive dispersion forces. Notable cases from carbocyclic chemistry are found in the conformations of 1,3,5-trineopentylbenzene (73JA5615; 74JA3190; 75JA6155; 76JA7515; 78JCS(2)1033) and the valence tautomerism in 1,4- and 1,6-di-*t*-butylcyclooctatetraene (81JA3232; 82JA4592). For a heteroaromatic example, consider the conformational situation in 4,5-dimethyl-*N,N'*-dineopentylimidazoline-2-thione (**79**) (86UP1 87JOC5177 (Scheme 59).

This molecule exists in two conformations, 93% syn and 7% anti at -70°C in solution, although the use of the intuitive repulsion approach would lead to the opposite assignment. The two *t*-butyl groups are approximately at the van der Waals distance in the syn form, and the only significant difference in energy between the syn and anti forms comes from the sum of all the small van der Waals attractions in the syn form making this conformer $\sim 4.6 \text{ kJ mol}^{-1}$ more stable. When the neopentyl groups are replaced by smaller alkyl groups, such as isobutyl or ethyl, the proportion of the syn conformer decreases, as expected, since these groups have fewer attractive contributions (Table VIII). When polar groups are introduced the electrostatic energy, positive or negative, is introduced. Thus, in *n,N'*-bis(trifluoroethyl)-5,5-dimethylthiobarbituric acid (Table VIII), electrostatic repulsion overbalances the van der Waals attraction. However, in this case the equilibrium is strongly dependent upon solvent polarity.



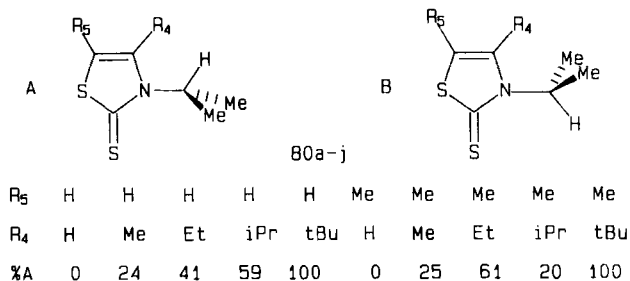
SCHEME 59

TABLE VIII
CONFORMATIONAL EQUILIBRIUM DATA FOR IMIDAZOLINE-THIONE AND
THIOBARBITURIC ACID DERIVATIVES^a

Compound	R	P syn %	ΔG° (kJ mol ⁻¹) (T, °C)
	<i>t</i> Bu	93	4.6(212)
	<i>i</i> Pr	59	0.25(151)
	<i>t</i> Bu	94	4.26(192)
	<i>i</i> Pr	75	1.42(157)
	Me	50	0(136)
	Adaman	88	3.34(202)
	Ph	46	-0.20(155)
	CF ₃	43	-0.38(166)

^a In (CD₃)₂ CO.

In Section III,B,2, we have shown that the conformational state of an isopropyl group can be used to determine the relative size of the flanking substituents. This approach is valid for spherical or cylindrical substituents, but application to polyhedral groups led to unexpected results. In 3-isopropyl- or 3-cyclohexyl- Δ^4 -thiazoline-2-thiones (**80a-j**), the isopropyl or cyclohexyl groups may adopt, as expected, two conformations (A and B) (Section III,B,2) (73MI4; 76JA2847; 76JA2853). In the 5-unsubstituted compounds, the population of rotamer A, determined by integration at low temperature by ¹H NMR, increases monotonically with the size of R₄ in the series R₄ = H, Me, Et, *i*Pr, *t*-Bu (Scheme 60). This behavior is expected from the accepted steric requirement of these substituents.

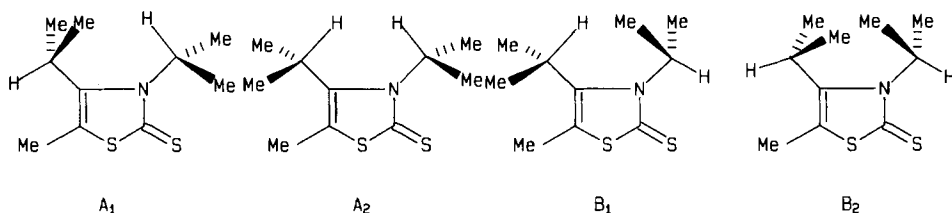


SCHEME 60

In the series of the 5-methyl analogues ($R_5 = \text{Me}$), the 4-methyl compound has the same population ratio as in the 5-H series: The 4-ethyl compound shows an increase in population A, whereas the 4-isopropyl compound (**80i**) shows a strong deviation from the monotonic series, giving 20% A instead of the expected 70% in acetone. If one strictly applies these data to the determination of the steric requirement of the flanking substituent, one might deduce that the 4-isopropyl group is "smaller" than methyl! The mutual interaction of the two isopropyl groups in **80i** gives rise to a particular behavior of these tetrahedral substituents. Strain energy calculations, taking only the van der Waals interactions into account, performed as a function of the angles Φ_1 and Φ_2 , which describe the rotations of the 3- and 4-substituents, result in an energy map of three main conformers: A_2 , B_1 , and A_1 (Scheme 61). Their presence was confirmed by experiment. In general, calculations on two geminal or vicinal isopropyl groups bonded to a planar framework implies the four energy minima depicted in Scheme 61.

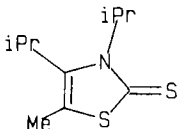
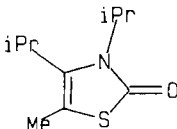
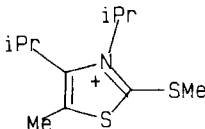
Their relative energy depends on the structure of the framework and on the sizes of the flanking groups, but generally the conformation A_1 and B_1 (gear-meshed conformations) are favored. A two-step rotational barrier (rotation of one isopropyl group and rotation of the other) was experimentally determined by DNMR. Modification of the steric requirements of the flanking substituents of the new structural block composed of two isopropyl groups results in a change in the relative population of the conformers and of the barriers to rotation (74TL3629) (Table IX). The barriers for the $B_1 \rightleftharpoons A_1 + A_2$ exchange process are, as expected, much more dependent on the size of the 2-substituent, whereas the barrier of the $A_1 \rightleftharpoons A_2$ process is little affected (Table IX).

The interdependence of these conformational states and the possibility of transmission of conformational modification through a series of interdependent conformational states led to the definition of the gear-effect: "a conformational transmission, which is caused by interaction between polyhedral substituents and which depends on their polyhedral shapes." As a corollary of this definition, it was possible to outline the difference between the gear-effect and the classical buttressing effect (76JA2847). The two effects depend on different modes of minimization of the steric strain introduced by two



SCHEME 61

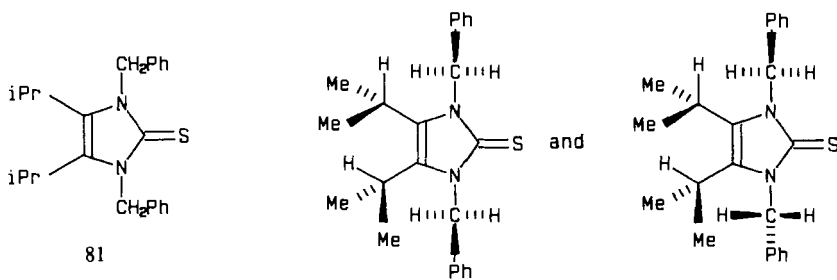
TABLE IX
BARRIERS TO ROTATION AND POPULATION OF CONFORMERS IN THIAZOLE DERIVATIVES^a

			
PA ₁	0.12	0.67	0.37
PA ₂	0.06	0.23	0.16
PB ₁	0.82	0.10	0.47
ΔG^\ddagger (B ₁ /A ₁ + A ₂)	68.97(299)	56.0(244)	65.6(298)
ΔG^\ddagger (A ₁ /A ₂)	49.7(226)	48.9(226)	53.9(226)

^a In CHCl₃ (74TL3629).

substituents in close contact. With spherical or cylindrical substituents, the major mode of strain minimization will be bond bending (buttressing effect), whereas with polyhedral substituents the major mode will be rotation of the groups (gear effect), though bond bending and other modes will also contribute. The term *static gear effect* was proposed (80MI2) for the meshing of alkyl groups in the ground state, and *dynamic gear effect* was proposed for special effects on the rate or mechanism of a process attributable to intermeshing of a chemical rotor with a neighboring group. Although the first definition has the advantage of being applicable to the majority of alkyl group interactions and to give new light on the problem of steric scales for polyhedral groups, a disadvantage is that the name leads the reader to expect true intermeshing states or coupled rotational processes. In short, the gear effect is a clear illustration of the fundamental problem of the conformational aspect of the steric requirement of polyhedral groups, which cannot be described by a single steric parameter.

The steric anisotropy created by two gear-meshed isopropyl groups is clearly demonstrated in 1,3-dibenzyl-4,5-diisopropylimidazoline-2-thione (**81**) (Scheme 62). In this apparently symmetrical molecule, three rate processes are observed (80JA7848). The high-energy process ($\Delta G^\ddagger_{229} = 48.0 \text{ kJ mol}^{-1}$) is the exchange of the isopropyl groups between two gear-meshed conformations of type A₁ and B₁ (Scheme 61). The two other processes are the rotations of the *N*-benzyl groups between perpendicular energy minima, as depicted in Section III,B,1. The barriers are quite different ($\Delta G^\ddagger_{205} = 44.3$ and 35.5 kJ mol^{-1}), because the two benzyl groups are in very different surroundings: One benzyl group rotates past the thiocarbonyl group and the other past the less bulky face of the isopropyl groups. This experimental evidence led to the definition of "Janus-groups," such as isopropyl, which



SCHEME 62

may be as bulky as a *t*-butyl or as small as a methyl, depending from which side they are considered. This clearly invalidates the use of a single parameter for the description of the size of polyhedral groups.

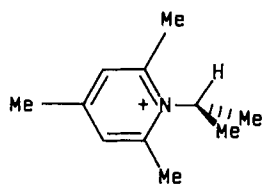
The methyl group is the smallest polyhedral substituent which can interact with its neighbors. Its intimate behavior is of primary importance for the quantitative treatment of steric effects, since it is often taken (as a combined atom) as a reference for the size of alkyl groups (Section II). The conformational aspect of the steric size of a methyl and its ability to induce conformational changes was clearly evident in the study of various poly-methylisopropylpyridines or -pyridinium salts **81a-e** (83T4209) (Scheme 63).

These examples, which are not limited to heterocyclic systems, provided a clear-cut case for the difference between buttressing and gear-effect, according to the definition given earlier. With substitution in a β -position one should expect, according to the buttressing concept, an increase in the apparent size of the α -methyl group. However, the induced conformational state of the methyl gives the opposite result. MINDO/3 calculations performed on **81** confirmed the importance of these induced conformational states (84T3971). MINDO/3 appears as a good method for the study of steric effect and conformations.

Geometry is a determining factor, since it is necessary to have close contact between the interacting isopropyl and methyl groups. In five-membered rings, such as thiazoline-2-thiones **82**, the conformational state of the isopropyl is not affected by substitution in position-5 by a R methyl, ethyl, or isopropyl group (76JA2847) (Scheme 64).

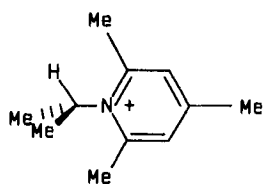
In 1-isopropylindole **83**, a 3-methyl group exerts no observable effect on the conformational state of the 1-isopropyl, but a 3-bromo substituent is large enough to induce through the 2-methyl a modification of the conformation of the isopropyl as in a pyridine series (84ACS(B)491). Clearly, conformational state and bond bending contribute to the resulting modification.

The conformational effect described in the previous paragraph results from the mutual interaction of two methyls which adopt a "gear-clashed" conformation when attached to a planar framework (83T4209; 84T3971)

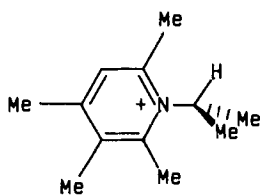


50

81a

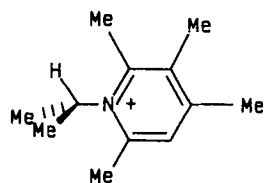


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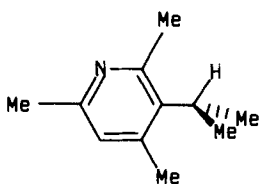


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81b

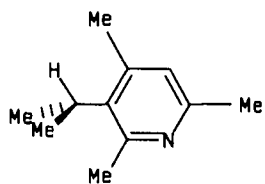


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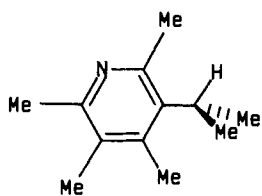


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81c

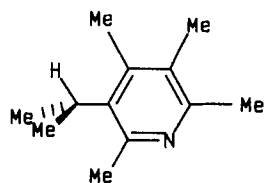


51%

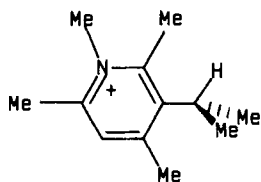


69%

81d

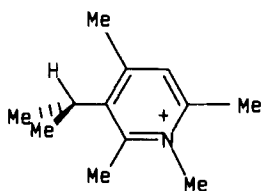


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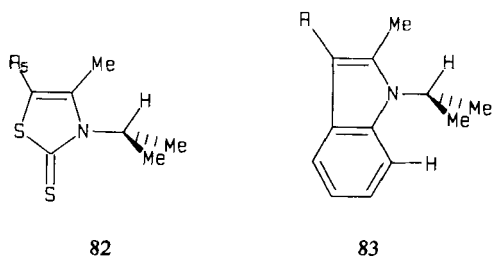
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81e

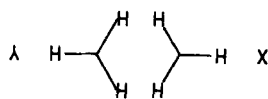


20%

SCHEME 63



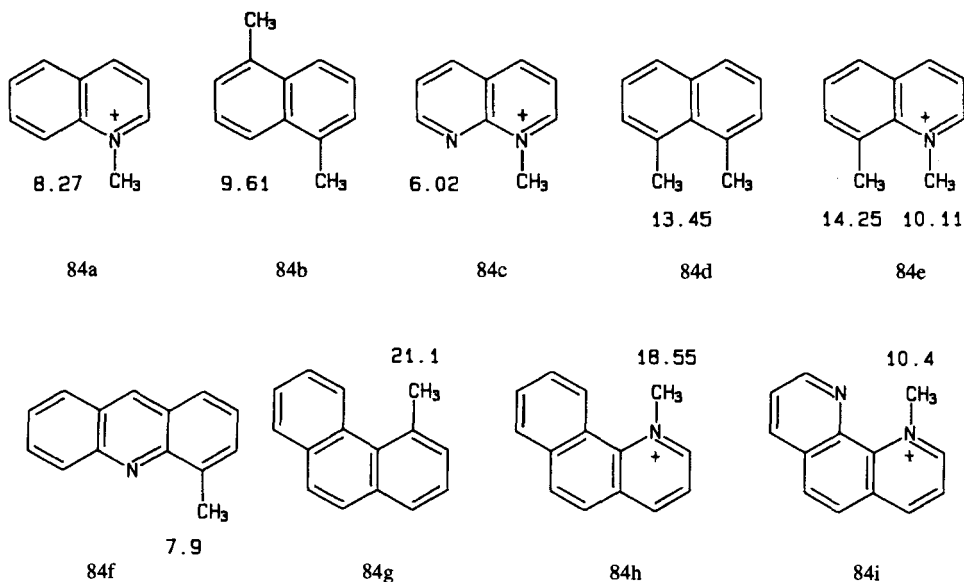
SCHEME 64



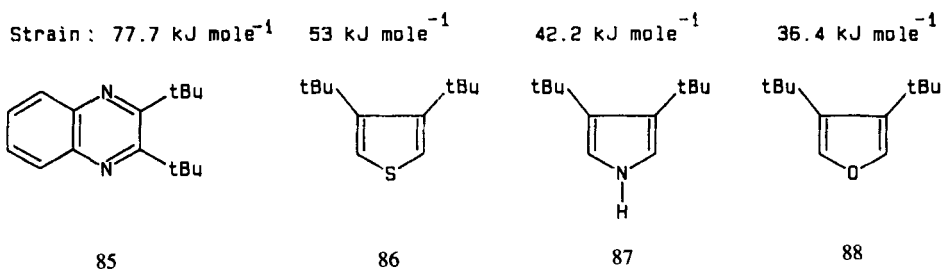
SCHEME 65. Gear-clashed methyls.

(Scheme 65). The conformational state and barrier to rotation of methyl groups have attracted much theoretical and experimental interest. The barriers to rotation of methyl in various aza aromatics have been determined in the solid state from ^1H -spin-lattice relaxation times (85JOC2972). Such barriers for **84a–i** are given (in kJ mol^{-1}) in Scheme 66.

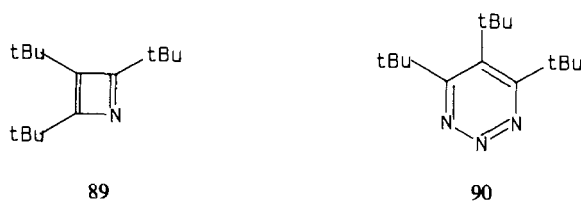
The barriers for methyl groups bonded to N- sp^2 atoms are smaller than the respective barriers for methyl bonded to C- sp^2 atoms in the corresponding carbon systems, suggesting facile bending of the N- sp^2 -CH₃ groups in the rotational transition state. The authors also compare the steric size of the lone pair of the nitrogen in **84c** and **84i** and, curiously, different values are obtained in terms of van der Waals radii.



SCHEME 66



SCHEME 67



SCHEME 68

The repulsion energies in various *o*-di-*t*-butyl heterocycles **85**–**88** were calculated using a simplified molecular mechanics approach (69T453) (Scheme 67). Here again, the importance of ring geometry is clear.

The highly strained heterocycles **89** and **90** (Scheme 68) have been prepared (86AG(E)842). Comparison of their properties with those of unstrained compounds would be instructive.

C. HINDERED ROTATION AND CONFORMATIONAL STATES OF SUBSTITUENTS ATTACHED THROUGH AN sp^2 -ATOM

Dynamic stereochemistry around an sp^2 – sp^2 -bond covers a wide range of energies, from the possibility of physical or chemical separation of atropisomers or stereoisomers down to very fast exchange between the various conformational states. The two main contributions to the change in potential energy accompanying torsion about sp^2 – sp^2 -bonds are the following: (1) the overlap between the p_z orbitals of the two sp^2 -atoms, namely the π -energy which has maxima at torsion angles of 90 and 270°; under these circumstances the stabilization is at minimum; (2) the steric repulsion with maxima at torsion angles close to 0 and 180°. In addition, through-space dipole–dipole interactions might be of importance in heterocyclic systems which exhibit

strong dipole moments and should be solvent dependent. Depending on the relative weight of these two components in the planar isomeric states (generally designated as *Z* and *E*) and in the perpendicular enantiomeric states, as well as the precise shape of the potential energy curves, different cases may arise. As proposed by Sandström for push-pull ethylenes (83MI1), very simplified curves in which the π -energy profile is represented by $0.5V_0$ ($[1 + \cos 2(\theta + 90^\circ)]$) and the steric profile by Gaussians give useful pictures of the general situations that may be encountered.

The barriers occurring at torsional angles close to 90° and 270° are called π -barriers (Fig. 8), whereas barriers occurring at torsional angles close to 0° and 180° (Fig. 9) are called steric barriers, even when they are far from being completely free from the other contribution.

Case 1. The π -barrier is larger than the steric barrier (Fig. 8). The two minima (which are generally split into enantiomeric forms) define stereoisomers of different energies which can be separated if the barrier to rotation is high enough. Steric effects will be reflected in the populations of the different isomers and in the angle of twist between the two planes. Steric effects will

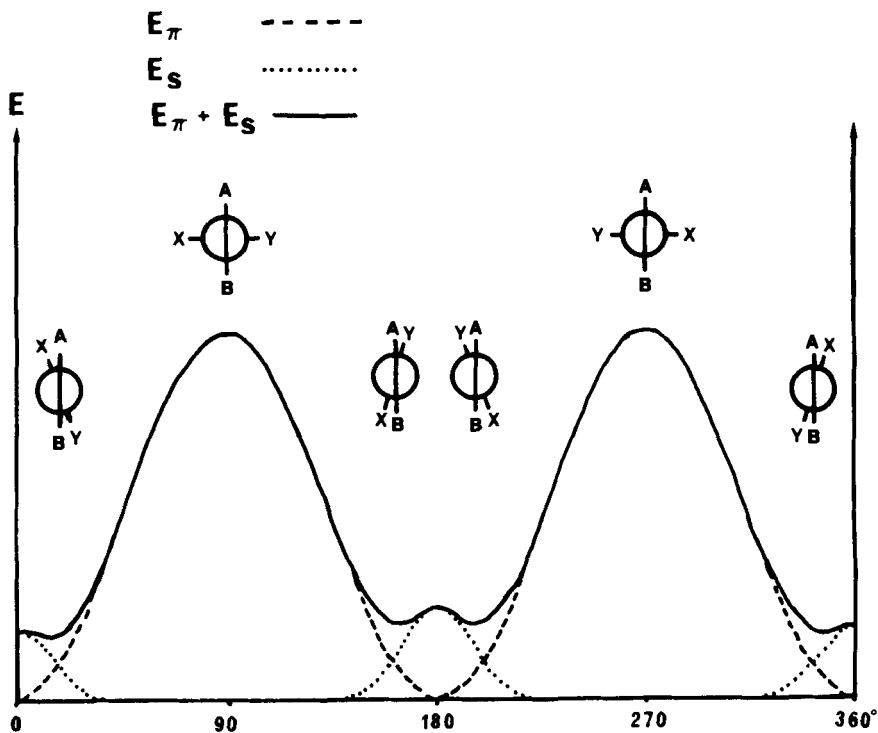


FIG. 8. Examples of π -barriers larger than steric barriers.

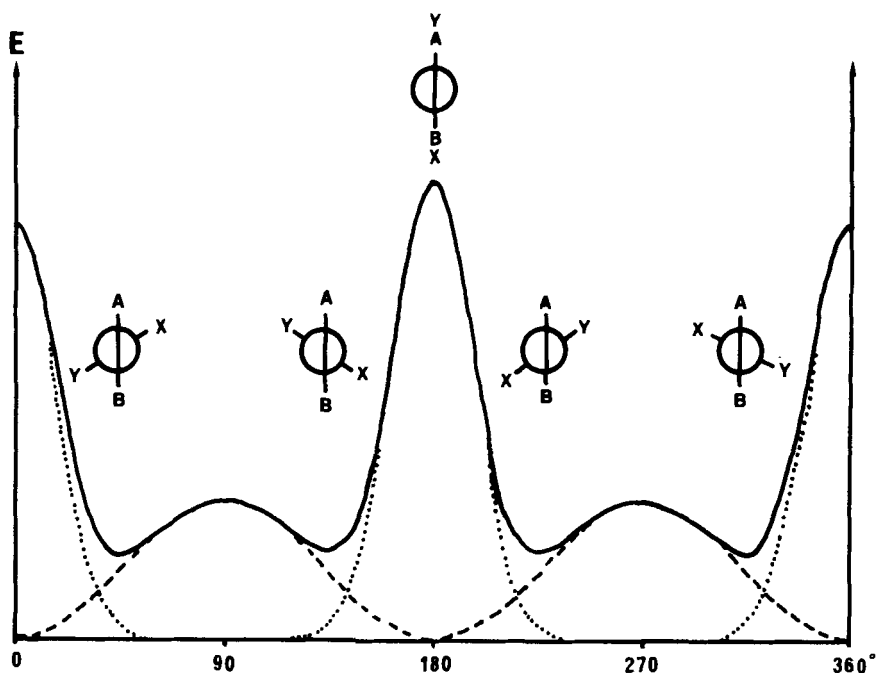


FIG. 9. Examples of steric barriers larger than π -barriers.

mainly affect the barriers to interconversions by a destabilization of the ground state.

Typical examples are barriers to rotation in dimethylamino heterocycles and barriers to rotation in heterocyclic amides and thioamides.

Case 2. The steric barrier is larger than the π -barrier (Fig. 9). The molecules are considerably twisted in the ground states. The ground states are enantiomers separated by achiral transition states. Thus, enantiomers could be obtained provided the barriers to their interconversion are high. Steric effects will mainly affect the energies of the transition states and to a lesser extent the ground-state interplanar angle. Typical examples are heteroarylbiaryl-like molecules with bulky ortho substituents.

All the situations between these two cases can be encountered with selective modification of the steric barrier at 0° compared to the one at 180° or by specific electronic stabilization of one stereoisomer. One interesting situation along the continuum ranging between the two extreme cases, obtained from suitable substitution and π -contribution, can result in the definition of two identifiable barriers (a steric one and a π one) of rather similar heights (77JA4526).

The π -contribution is dependent on the whole molecular system, which composes the two planar parts linked by the sp^2-sp^2 -bond and thus long-range electronic substituent effects contribute to the energy profile in addition to the intrinsic electronic properties of the two planar partners. Proximity effects are responsible for the steric contribution and, as pointed out for sp^2-sp^3 -stereochemistry, heterocyclic compounds afford a large variety of geometrical situations which are of the utmost interest for the study of steric effects.

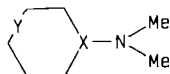
Since it appears from the previous comments that the dynamic stereochemistry is influenced by two main contributions, electronic and steric, special care must be taken in the separation of these for the quantitative determination of the steric contribution.

1. Typical Examples of π -Barriers

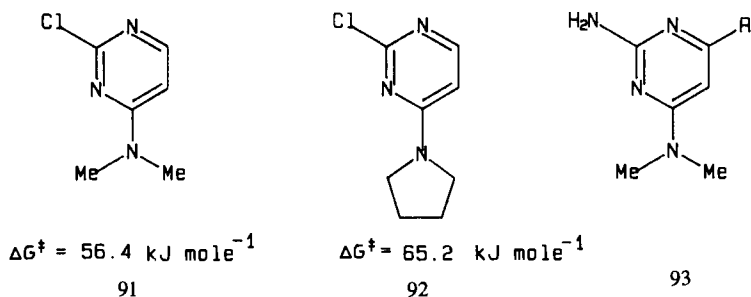
a. *Hindered Rotation around C—N Bonds. i. Heteroaromatic amines.* Heteroaromatic amines as well as aromatic amines exhibit partial double bond character for the C—N bond, due to conjugation of the nitrogen lone pair with the aromatic ring. Conjugation is suppressed in the transition state for rotation and gives rise to a typical π -barrier. A series of dimethylamino heteroaromatic compounds has been studied by various authors and their barriers to rotation determined by DNMR. In the absence of an ortho-steric effect, the difference in barrier heights reflects a difference in bonding interaction between the dimethylamino group and the heterocyclic ring system. As expected, π -electron-deficient heterocycles exhibit higher barriers than π -electron-rich heterocycles. The barriers range from 7.6 kcal mol⁻¹ (31.8 kJ mol⁻¹) in 2-dimethylaminopyridine (69CC933) to 21.8 kcal mol⁻¹ (81.5 kJ mol⁻¹) in 4-dimethylamino-2-methyl-6-phenylpyrylium salt (79OMR71). These values are larger than the one estimated for dimethylaminobenzene (21.3 kJ mol⁻¹) (70CC1299).

A dimethylamino group presents a steric effect which destabilizes the ground state compared to the steric-free pyrrolidino group (72JCS(P2)451). This is clearly shown in the large difference in experimental barriers in pyrimidine derivatives **91** and **92** (72JCS(P2)451) (Scheme 70).

However, multiplicity of the signal for the pyrrolidino group gives rise to difficulties in the experimental determination of the barrier by DNMR and



SCHEME 69



SCHEME 70

thus most of the studies were performed on a dimethylamino group although the observed barrier is not free from steric effect.

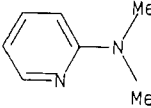
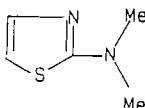
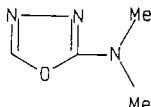
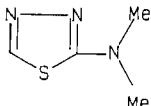
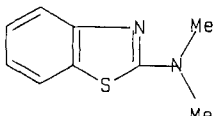
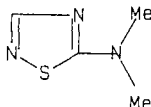
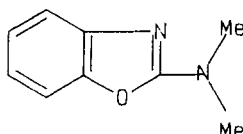
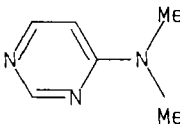
Reported in Table X are selected barriers to rotation in the "absence" of steric effects. From these values, electron-accepting substituents in a nonortho position increase whereas electron-donating substituents decrease the barriers (74OMR144; 77TL4525) as observed in aniline derivatives (70CC1299; 80JCS(P2)1704). Substituent effects have been studied in pyrimidine 93 (82OMR274). Cross conjugation with substituents having lone-pair electrons decreases the barrier to rotation. For nitrogen-containing heterocycles, protonation at one ring nitrogen enhances the barriers to rotation by increasing the electron attraction of the ring (65JA5575; 75JCS(P2)1776; 79JCS(P2)330; 79OMR159; 85JCS(P2)1513).

A correlation has been found between the observed barriers and the π -bond order of the C—N bond calculated by CNDO/2 (79JCS(P2)330). We believe that having this correlation for a given π -bond order and knowing the deviation from this correlation could provide a quantitative estimate of steric interaction in the ground state. This basic correlation affords the possibility of separating electronic and steric effects.

A ^{13}C —NMR study of several dimethylamino derivatives of pyridine, pyrimidine, and 2-oxopyrimidine with and without *o*-methyl substitution indicates a progressive twist of the dimethylamino group in hindered derivatives (78JCS(P2)1119). Unfortunately, the barriers have not yet been determined. The free energy of activation for 4-(*N*-methylamino)pyridine (80JCS(P2)1704) is $\Delta G^\ddagger = 42.6 \text{ kJ mol}^{-1}$ and is close to that of *N*-methyl-4-nitroaniline.

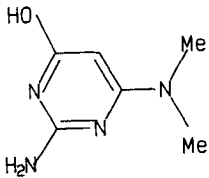
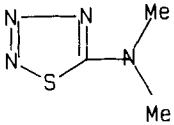
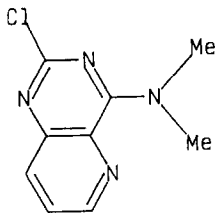
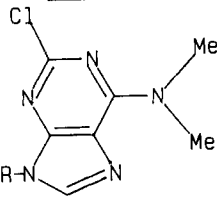
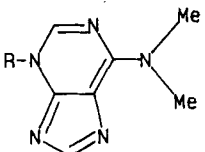
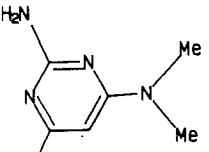
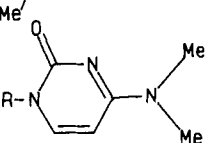
A clear example of steric intervention is provided by a DNMR study by Riand and co-workers (79JCS(P2)1248) on 4-dimethylaminopyrimidine **94**. Substitution of the hydrogen by a methyl group in the 5-position results in a 25 kJ mol^{-1} lowering of the barrier. This value includes the electron-donating effect of the methyl group, which cannot account for the observed

TABLE X
SELECTED BARRIERS TO ROTATION AROUND THE C—N BOND IN DIMETHYLAMINO
HETEROAROMATICS IN THE ABSENCE OF A STERIC EFFECT

Compound	ΔG^\ddagger (kJ mol ⁻¹) (T, °C)	Solvent	Reference
	31.8(133)		(69CC933)
	32.2(150)	CHClF ₂	(77TL4525)
	< 34.3(200)	Pyr-d ₅ /CD ₂ Cl ₂	(74OMR144)
	34.3(200)	Pyr-d ₅ /CD ₂ Cl ₂	(74OMR144)
	47.46(298)	(CD ₃) ₂ CO	(85JCS(P2)1513)
	48.5(200)	Pyr-d ₅ /CD ₂ Cl ₂	(74OMR144)
	50.39(298)	(CD ₃) ₂ CO	(85JCS(P2)1513)
	51.0(298) 53.5(247)	CHCl ₃ CD ₃ OD	(69OMR57) (79JCS(P2)1248)

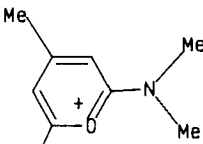
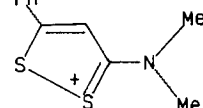
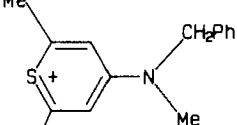
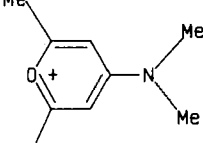
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TABLE X (Continued)

Compound	ΔG^\ddagger (kJ mol ⁻¹) (T, °C)	Solvent	Reference
	52.7(230)	CDCl ₃	(82OMR274)
	53.1(248)	Pyr-d ₅ /CD ₂ Cl ₂	(74OMR144)
	56.5(278)	CDCl ₃	(72JCS(P2)451)
	56.0(273)	CDCl ₃	(67CC1275)
	63.9(303)	CDCl ₃	(68CC1002) (75JA885)
	61.4(276)	CDCl ₃	(82OMR274)
	62.3(283)	CDCl ₃	(72JPC64)

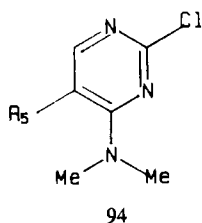
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TABLE X (Continued)

Compound	ΔG^\ddagger (kJ mol ⁻¹) (T, °C)	Solvent	Reference
	77.8(298)	CH ₃ NO ₂	(79OMR71)
	77.8(349)	DMSO-d ₆	(71BSF2607)
	81.5(298)		(75MI2)
	91.2(360)	CH ₃ NO ₂	(79OMR71)

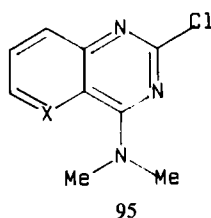
value. In quinazoline **95a**, benzo annelation has the same effect on the barrier as methyl substitution (72JCS(P2)451).

The higher barrier in pyrido(3,2-*d*)pyrimidine **95b** was mainly attributed to the difference in steric requirements of the peri hydrogen (**95a**) and the



a $R_5 = H$ $\Delta G^\ddagger = 57.3 \text{ kJ mole}^{-1}$

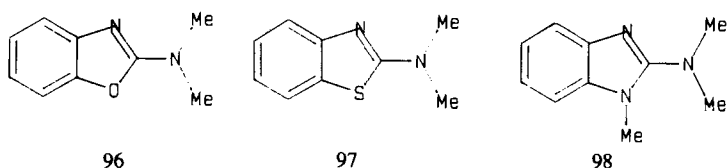
b $R_5 = Me$ $\Delta G^\ddagger = 32 \text{ kJ mole}^{-1}$



a $X = C-H$ $\Delta G^\ddagger = 34.7 \text{ kJ mole}^{-1}$

b $X = N$ $\Delta G^\ddagger = 56.5 \text{ kJ mole}^{-1}$

SCHEME 71



SCHEME 72

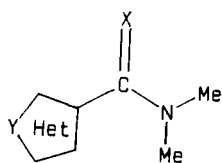
lone-pair of the nitrogen (**95b**) leading to the statement “in terms of steric requirement, one may consider the lone-pair of the pyridine nitrogen atom as smaller than an aromatic hydrogen atom” (72JCS(P2)451). As pointed out earlier, one has to take into account the difference in electron-accepting abilities of the heterocycles and we believe that a large part of the observed difference may be explained on that basis. An argument in favor of our explanation is provided by the striking similarity in the differences in barriers on going from a dimethylamino group to a pyrrolidino group in quinazoline **95a** and pyridopyrimidine **95b**: $\Delta\Delta G^\ddagger = 25.9 \text{ kJ mol}^{-1}$ in the former and 25.4 kJ mol^{-1} in the later. A difference in the steric requirement of the framework for a constant difference in the steric requirement of the rotating group should give a difference in the sensitivity of the interaction expressed by $\Delta\Delta G^\ddagger$. In the absence of a marked steric effect of the framework as it is in pyrimidine itself, the barrier change going from a dimethylamino group to a pyrrolidino group is 10 kJ mol^{-1} .

A study (85JCS(P2)1513) of the barrier to rotation in 2-dimethylamino-benzoxazole **96**, -benzothiazole **97**, and -*N*-methylbenzimidazole **98** gives a clear-cut case of steric intervention in the latter compound. The dimethylamino group is twisted by 40° with respect to the plane of the heteroaromatic ring in **98** and this is the origin of the lack of any change in NMR signal down to 127 K. Compounds **96** and **97** without the *o*-methyl group have normal π -barriers (Scheme 72) (Table X).

ii. *Heteroaromatic amides and thioamides.* The π -barriers to rotation around the C—N bond of amides and thioamides have been the subject of numerous investigations and reviews (70CRV517; 75MI1; 78JA1500; 79TL639).

Particularly interesting are the barriers to rotation of the dimethylamino group in heteroaromatic amides and thioamides which can be used as a sensor for the following effects (Scheme 73).

1. A cross-conjugation effect of the heteroaromatic, which lowers the barrier to rotation by π -conjugation of the π -heteroaromatic with the carbonyl group in the transition state. Thus, in the absence of a steric effect, the free energies to rotation of the $\text{CON}(\text{Me})_2$ moiety bonded to a variety of

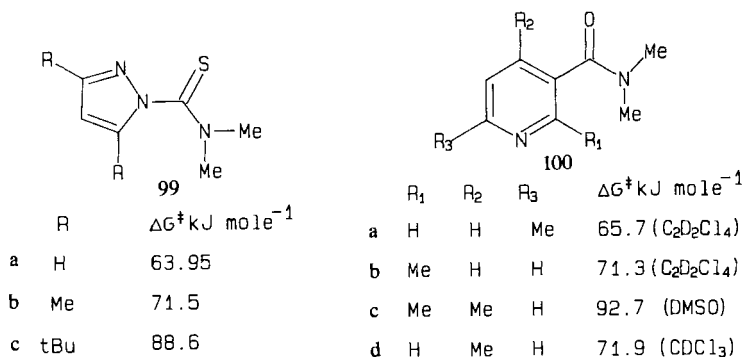


SCHEME 73

5-membered heteroaromatics was used as a tool for assessing the conjugation capabilities of these heterocycles (74JOC2806; 74T4129; 76JOC3591; 77T1337). The data for thiophene, furane, isoxazole, and thiazole are given in Table XI. Solvent effects have also been studied (85JCR(S)108).


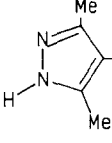
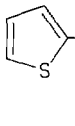
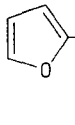
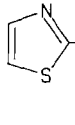
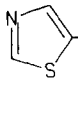
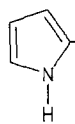
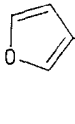
2. A steric effect of the heteroaromatic, directly related to geometry, prevents cross-conjugation by twisting the amide or thioamide group out of the ring in the ground state and in the transition state. In the ground state, the heterocycle is not coplanar with the carbamide moiety. For instance, in nicotinamide the amide group is planar and its plane is twisted by an angle of 33° from the plane of the pyridine, according to LCAO-MO calculations (72CCC2933). X-Ray data give a 24° torsional angle (54AX283), very similar to the one found in benzamide (59AX130; 73MI3). This particular secondary steric effect raises the barrier to rotation of the amido group. Particularly bulky ortho substituents may even hinder the rotation of the dimethylamino group by direct through-space interaction with the methyl groups in the transition state. Since we are dealing with a remote steric effect, this is a case in which the typical π -barrier is enhanced by a remote steric contribution.

Typical examples of the intervention of steric effects are provided by the studies on pyrazoles **99a-c** (72ACS21) or on substituted nicotinamides **100a-d** (75CB730) (Scheme 74).



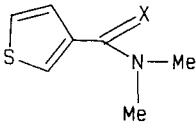
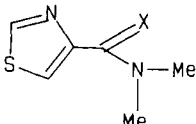
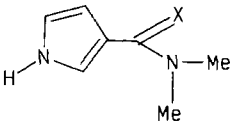
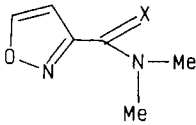
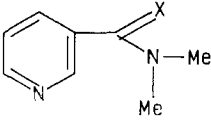
SCHEME 74

TABLE XI
SELECTED BARRIERS TO ROTATION AROUND THE C—N BOND IN
HETEROCYCLIC (THIO)AMIDES WITHOUT AN ORTHO STERIC EFFECT

Compound	ΔG^\ddagger (kJ mol ⁻¹)	Reference
	64.4 (X = S)	(72ACS21)
	71.8 (X = S)	(77OMR117)
	59.11 (X = S)	(77T1337)
	57.7 (X = O)	(77T1337)
	60.7 (X = O)	(76JOC3591)
	61.3 (X = O)	(77T1337)
	63.2 (X = O)	(76JOC3591)
	76.1 (X = S)	(77T1337)
	71.6 (X = O)	(77T1337)
	59.6 (X = O)	(77T1337)
	60.2 (X = O)	(76JOC3591)
	64.8 (X = S)	(77T1337)
	61.3 (X = O)	(77T1337)
	63.2 (X = O)	(76JOC3591)

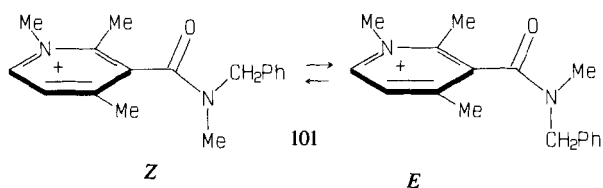
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TABLE XI (Continued)

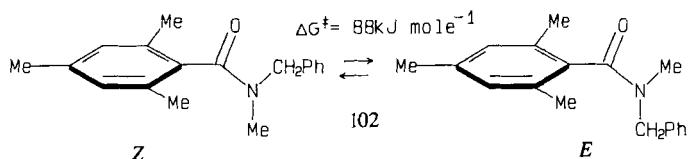
Compound	ΔG^\ddagger (kJ mol ⁻¹)	Reference
	57.0 (X = O)	(77T1337)
	75.24 (X = S) 67.0 (X = O)	(77T1337)
	61.1 (X = O)	(76JOC3591)
	75.3 (X = O)	(77T1337)
	66.4 (X = O)	(75CB730)

A methyl or a *t*-butyl substituent in **99** in an ortho position dramatically increases the barrier. Thus, for a given model the modification of the barriers can be used to determine a steric scale of substituents in this particular geometrical context provided the electronic contribution of the substituent on the cross-conjugation capability of the heterocycle can be determined. This approach can be applied with success to the steric effect of alkyl groups whose electronic contribution should be very similar.

Remote steric effects of the methyl groups in 2,4-positions are responsible for the high barrier to rotation around the C—N bond in carbamoylpyridinium iodide **101**. The rotameric distribution remains constant in D₂O for several days but appears to be affected by the temperature at which the



SCHEME 75



SCHEME 76

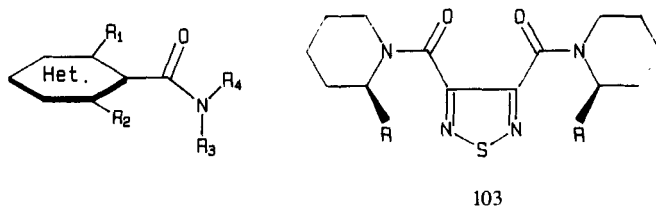
quaternization of the parent pyridine was performed. Equilibration in D_2O leads to a ratio $Z/E = 1.7$ (60°) (86CC546).

The barrier to rotation in **101** was not given but it can be interestingly compared to the one determined in the isosteric carbocyclic compound **102** ($\Delta G^\ddagger \approx 89.9 \text{ kJ mol}^{-1}$) (65AG(E)935) (Schemes 75 and 76).

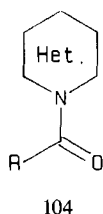
The Z/E ratio in **101** is similar to the one found in the thioamide analogue of **102** (≈ 2.1), which was successfully separated into isomers ($\Delta G^\ddagger_{Z-E} = 114.1 \text{ kJ mol}^{-1}$) (65AG(E)935; 68CB864).

Substitution in the ortho positions of the heteroaromatic ring progressively increases the interplanar angle between the heterocycle and the carbonyl plane and thus gives rise, with sufficient substitution, to a steric barrier around the heteroaromatic amide bond similar to that encountered in biphenyls. The transition state to rotation around this bond may be even higher than that for rotation around the C—N bond (*vide infra* Section III,C,2) (Scheme 77).

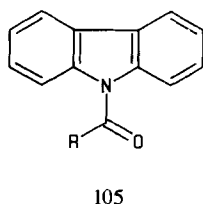
The conformations in the crystalline state and in solution have been studied for the sterically congested diamides **103** (86HCA389).



SCHEME 77



SCHEME 78



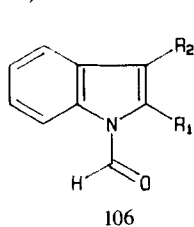
	R	ΔG^\ddagger kJ mole ⁻¹
a	H	62.2
b	Me	39.3
c	Et	40.1
d	iPr	40.9
e	tBu	undetected

SCHEME 79

The π -barriers to rotation in **104** (Scheme 78) in which the nitrogen atom belongs to a heteroaromatic, are particularly low for amides. Delocalization of the nitrogen electron pair within the heteroaromatic system in the transition state accounts for the observed low barriers. Under steric perturbation in X, R or in orthopositions of the heterocycle, the π -barriers will be greatly affected and the high-energy process will become a steric barrier with a planar transition state. Illuminating examples are provided by a ¹³C-DNMR study of torsional barriers in *N*-acylcarbazoles **105a–c** (79JCS(P2)1045). When the formyl hydrogen is replaced by an alkyl substituent, the stabilization of the ground state is reduced. The values of the barriers do not change in an appreciable manner in the series Me, Et, *i*Pr, suggesting a conformational effect of the acyl group which can adopt a relatively non-hindered conformation. For *R* = *t*-Bu, the π -barrier is not detectable and an LSR study shows that in the ground state the acyl group is almost perpendicular to the ring (79JCS(P2)1045)(Scheme 79).

Some selected examples of π -barriers are given in Table XII. Conformational states of *N*-acetyl derivatives of pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, indole, benzimidazole, benzotriazole, indazole, and tetrazole have been studied by ¹³C NMR (78JCS(P2)99). In some cases, the occurrence of only one isomer precludes the determination of the barrier, as for 1-acetylpyrazole (74BSF1137) and 1-acetylindoles (75OMR445).

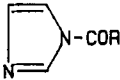
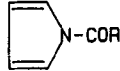
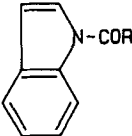
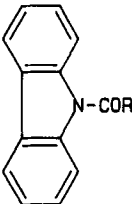
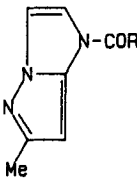
A DNMR study of formyl indoles **106a–c** in CDCl₃ reveals the intervention of both electronic and steric contributions (75OMR445; 86JIC216) (Scheme 80).



	R ₁	R ₂	ΔG^\ddagger kJ mole ⁻¹
a	H	H	E → Z 61.5 Z → E 63.1
b	H	Me	E → Z 68.1 Z → E 70
c	Me	Me	E → Z 60. Z → E 66.1

SCHEME 80

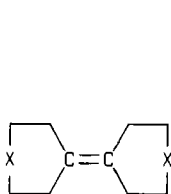
TABLE XII
SELECTED π -BARRIERS IN *N*-ACYL HETEROCYCLES

Compound	R	Solvent	$\Delta G_{\pi}^{\ddagger-z}$ (kJ mol ⁻¹)	Reference
	Me	CHCl ₂ F	44.0	(74CJC2744)
	H Me	CDCl ₃ CDCl ₃	~ 58 50.5	(69CC501) (73CR(C)1163) (69JPC4124)
	H	CDCl ₃	61.5	(75OMR445)
	H	THF	62.0	(75OMR445) (79JCS(P2)1045)
	Me	CDCl ₃	62	(74CJC2744)

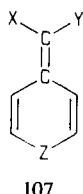
The similarity of the barriers to rotation in **106a** and **106c** results from two opposite contributions of the methyl groups in **106c**. The two methyl groups are electron donating and thus they should raise the π -barrier as clearly seen in **106b**. The methyl group in the ortho position exerts a steric effect, which reduces the observed barrier by destabilization of the ground state.

The relative variation of the barriers on going from formyl to acetyl could be used in principle as a sensor for the steric requirement of the framework. This method has to be applied under isoelectronic conditions.

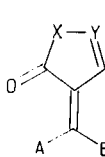
b. *Hindered Rotation around C—C Bonds.* The stereodynamics of push-pull and strained ethylenes have been reviewed (83MI1) and the factors affecting the π -barriers and steric barriers thoroughly discussed (Scheme 81).



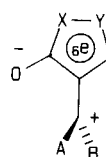
SCHEME 81



107



108



109

SCHEME 82

Table XIII gives typical examples of π -barriers for planar heterocycles comparing the electron-attracting or electron-donating moiety to push-pull ethylenes. Steric effects destabilize the ground state and thus greatly reduce the π -barriers to rotation. In these push-pull ethylenes the large entropy of activation and solvent effects hampered easy comparison of the barriers without high-quality determination of the activation parameters.

In 4-heterocyclohexadienes **107** ($Z = O, S,$ or NR), the low π -barrier is partly due to the formation of pyrylium, thiapyrylium, or pyridinium ions in the transition state for $C=C$ rotation (77JOC2734). The barrier-lowering effect of Z is increasing in the series $O < S < NR$. Reasonably linear Hammett plots are obtained when ΔG^\ddagger (298 K) for the $C=C$ rotation is correlated with σ^- for one of the groups X and Y , keeping the other constant, indicating that steric effects are small and essentially constant (Scheme 82).

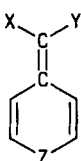
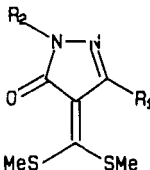
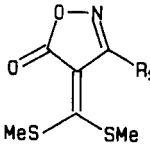
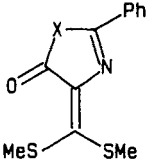
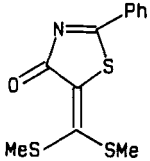
In five-membered ring compounds **108**, the heterocyclic rings adopt an aromatic electronic structure in the transition state **109**. The steric effect of R_1 (Table XIII) destabilizes the ground state of the pyrazolones and isoxazolones, whereas the lack of such substituents contributes to the higher barriers in the oxazolone and thiazolone. The height of the $C=C$ barrier cannot be taken as a measure of the tendency of the respective ring systems to adopt an aromatic electronic structure, since ground-state stabilization also plays an important role in determining the barrier.

Strained ethylenes, which lack the push-pull effect, may show very interesting stereochemistry and their thermochromic and photochromic properties have been the subject of considerable attention. The heterocyclic compounds **110a-b** adopt in the ground state an anti-folded conformation, with a slight pyramidalization of the linking sp^2 -atoms. The stereochemistry of these compounds, as well as the related twisted bifluorenylidene **111**, has been studied thoroughly by Agranat and co-workers (76JA615; 77NJC361; 78JA5604; 79JA665; 79JOC1949; 79NJC59) (Scheme 83).

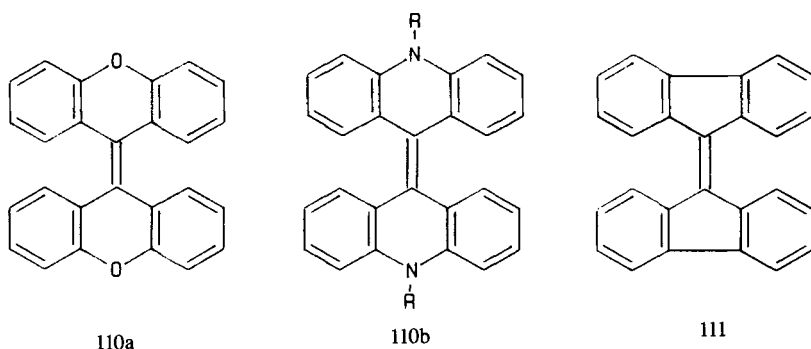
The conformational behavior of these compounds involves several steric and π -barriers separating twisted or folded intermediates. The similarity in steric and π -barriers makes it difficult to separate steric from electron effects.

c. *Conclusion.* After this survey of typical π -barrier, it appears that steric effects obviously play a role in the barrier height. By definition, the main

TABLE XIII
SELECTED π -BARRIERS IN PUSH-PULL ETHYLENES WITH HETEROCYCLIC DONORS AND ACCEPTORS

Compound	X	Y	Z	ΔG^\ddagger (kJ mol ⁻¹) (T, °C)	Solvent	Reference
	NO ₂	Ac	O	57.7(298)	CD ₃ CN	(77JOC2734)
	NO ₂	Ac	S	48.5(298)	C ₃ D ₆ O	(77JOC2734)
	NO ₂	Ac	NBu	< 36.4(183)	C ₃ D ₆ O	(77JOC2734)
	<div> <div>R₁</div> <div>R₂</div> </div>					
	Me	Me		89.9(403)	ODC	(78OMR555)
	Ph	Me		75.6(366)	ODC	(78OMR555)
	Me	Ph		78.6(358)	ODC	(78OMR555)
	<div> <div>R₁</div> </div>					
	Me			78.6(347)	ODC	(74MI1)
	<div> <div>X</div> </div>					
	O, S			> 105		(74MI1)
				> 105		(74MI1)

contribution comes from the π -system, and thus a clean separation of steric and electronic contributions is always difficult to ascertain. The most suitable models are those in which the intrinsic π -barrier is minimal. Table X–XIII can be used to select such models.

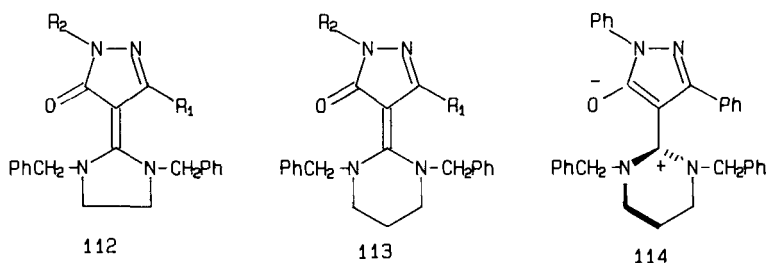


SCHEME 83

2. Typical Examples of Steric Barriers around sp^2-sp^2 -Bonds

a. Twisted Push-Pull Ethylenes. Push-pull ethylenes, as discussed previously, exhibit low π -barriers due partly to the particular electronic stabilization of the zwitterionic transition state at 90 and 270°, but also to steric destabilization of the more or less planar ground state. When the steric requirement of the substituents are further increased, the steric barrier may become larger than the π -barrier. The literature on such twisted ethylenes has been reviewed (83MI1).

In **112** and **113**, a high steric barrier is obtained by the two ring-closed parts of the molecule, which prevents out-of-plane twist within each half of the molecule (Scheme 84).



R_1	R_2	$\Delta G^\ddagger \text{ kJ mole}^{-1}$	$\Delta G^\ddagger \text{ kJ mole}^{-1}$	$\Delta G^\ddagger \text{ kJ mole}^{-1} = 106$
CH ₃	CH ₃	66.9	--	
CH ₃	Ph	68.1	--	
Ph	CH ₃	75.6	95.3	
Ph	Ph	76.5	99.1	

SCHEME 84

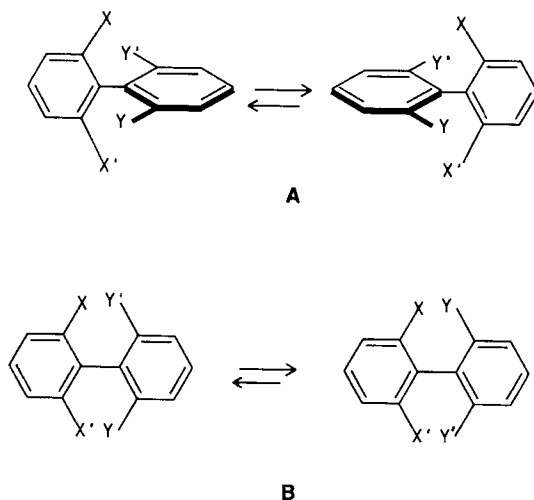
In a low-temperature NMR spectrum of **112** and **113**, where passage over the steric barrier at 0° (180°) is slow, the geminal methylene protons in the benzyl groups are diastereotopic, which unequivocally shows that the molecules are twisted. If the observed rate process were over the π -barrier with an effectively planar ground state, the two benzylic methylene groups would give rise to two singlets instead of the observed single AB-quartet.

Even more complicated systems arise when the π -barrier and the steric barrier are of equal magnitude, in which case a four-site exchange is observed. No such example incorporating heteroaromatics has, however, appeared (82MI5).

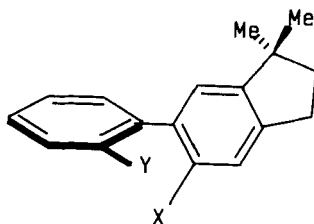
Considering the high barrier of **113** ($R_1 = R_2 = \text{Ph}$), the design of a stable chiral molecule is straightforward. Thus, the chiral, twisted ethylene derivative **114** has been resolved by chromatography on triacetylcellulose (82TL4237).

The quantitative separation of the energy in steric and electronic contributions in these systems is difficult and theoretical calculations of stable conformers and barrier heights are not yet feasible.

b. Heterocyclic Analogues of Biphenyl. The study of the conformational state and dynamical processes in biphenyls has been a cornerstone in the quantitative treatment of the steric effects (32JA4426; 33CRV161; 56MI2; 62MI1; 69MI1). The through-space interactions between ortho substituents are at a maximum when the two rings are coplanar and at a minimum in an orthogonal conformation (Scheme 85).



SCHEME 85. Ground state for a high (A) or low (B) steric barrier.



SCHEME 86

Nonsteric contributions may affect the barriers: (1) the electronic effect of the substituent which modifies the conjugation in the planar state; (2) the eventual interaction between ortho substituent and the π -cloud of the second ring in the perpendicular state; (3) dipole–dipole interactions in the planar state; (4) hydrogen bonding or complexation in the planar transition state.

Depending on X, X', Y, and Y', atropoisomers may result and the barriers are accessible according to the energy range, by resolution–racemization, or by DNMR on suitably labeled compounds.

Sternhell *et al.* (80JA5618), in a rationally designed system for a DNMR study of **115**, have determined quantitatively the steric requirement of a wide variety of substituents and derived their effective van der Waals radii (Scheme 86).

The rotational barriers are the sum of additive contributions designated “interference value between H and X,” which can be used to predict rotational barriers. An interesting equation has been derived [Eq. (7)].

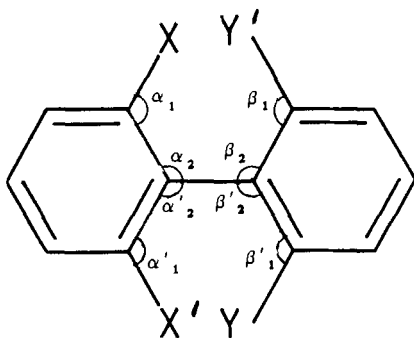
$$\Delta G_{340}^{\ddagger} = 26 \Sigma r^* + 4.7 \text{ kJ mol}^{-1} \quad (7)$$

which relates the barriers to a simple geometrical parameter Σr^* . Equation (7) has been replaced subsequently by Eq. (7') (87JA341).

$$\Delta G_{340}^{\ddagger} = 30.7 \Sigma r^* - 8.2 \text{ kJ mol}^{-1} \quad (7')$$

These equations are not securely based since they do not discriminate between the different shapes of the potential function of the interacting groups and the energy associated with bending and stretching, but they are useful for a rough estimate of the barriers in related models. Molecular mechanics calculations are certainly more reliable in this respect (74ACR345; 82MI5).

Heterocyclic analogues of biphenyls have naturally given rise to considerable interest, since many physical and chemical properties (UV, ^{13}C NMR, dipole moment, $\text{p}K_a$) depend on the relative conformation of the two planar rings. Heterocyclic analogues provide a large variety of geometrical situations in addition to the differences in conjugation which are impossible in carbocyclic analogues. For instance, the interannular distance is $\text{C}—\text{C} = 1.48 \text{ \AA}$ in biphenyls (71T991), $\text{N}—\text{C} = 1.40 \text{ \AA}$ in *N*-phenylazoles (78T1139),



SCHEME 87

and $N-N = 1.36 \text{ \AA}$ in N,N -linked biazoles (84CJC687). In addition, the bond angles α_1 or α_2 , $\alpha'_1\alpha'_2$, $\beta_1\beta_2$, $\beta'_1\beta'_2$, which are decisive in determining the resulting distances between the interacting groups, vary widely from six-membered rings to five-membered rings with different heteroatoms (Scheme 87).

Compared to the extraordinary potential of these heterocyclic analogues of biphenyl in the study of steric effects, relatively few barrier determinations have been performed.

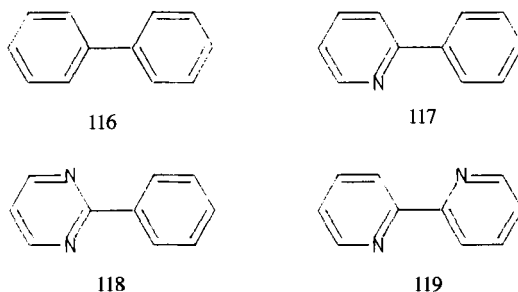
However, a considerable number of articles have been devoted to the experimental and theoretical determination of the interannular angles in the equilibrium conformation of aryl heterocycles, and of heteroaryl-heteroaryl systems composed of identical or different heterocycles. A full critical analysis of these studies and the techniques used is beyond the scope of this article. However, we discuss some general trends which emerge in the absence of ortho substituents and which are useful for the separation of conjugation and intrinsic steric effects in the heterocycles.

i. *Six-membered ring bonded to a six-membered ring.* The dihedral angle in biphenyl has been determined by different groups. The value depends upon the method and the experimental conditions: 0° in the crystal (61AX1135), 34° in liquid crystalline solvent (73JCS(P2)1396), 38° in acetonitrile (65ZN1117), $30-40^\circ$ in benzene (53JCS2456), 37° in CS_2 (86JPC1752), 42° (49ACS408; 58MI2), 52° by EHT calculations (78T1139), and 45° by NDDO calculations (75ZC23). In a series of studies by gas-phase electron diffraction, Bastiansen *et al.* concluded that the average torsional angle for the non-ortho-substituted biphenyl derivatives is $44.3 (0.4)^\circ$ and is insensitive to substitution in the meta and para positions. The π - and steric barriers seem to be approximatively equal to 6 kJ mol^{-1} (85JST59; 85JST77; 85JST95; 85JST115).

Murrell and co-workers (65RTC1399) have compared the NMR spectra of azabiphenyls and have shown that coplanarity increases in the series biphenyl (116), 2-phenylpyridine (117), 2-phenylpyrimidine (118), and 2,2'-bipyridyl (119). It was deduced that the through space $C-H\cdots N$ interactions are weaker than the $C-H\cdots H-C$ ones (Scheme 88).

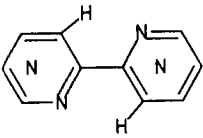
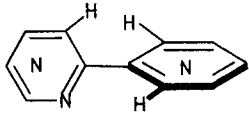
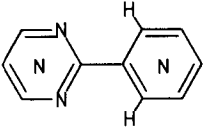
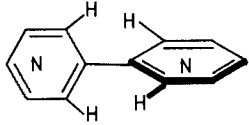
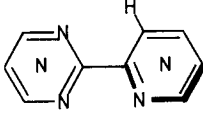
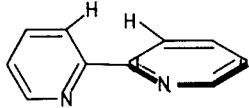
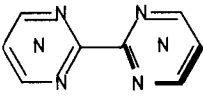
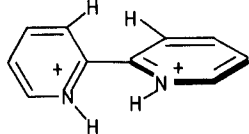
The same trend is well preserved in the extended Hückel calculations of the twist angle in isomeric phenylpyridines and isomeric bipyridines. The smaller angles are obtained for 2-phenylpyridine and 2,2'-bipyridine, respectively (71T991). Semiempirical calculations taking into account π -energy, dipole-dipole interaction, and strain and deformation energies confirm this trend for 2,3'-bipyridine (83MI3). CNDO/2 calculations are inadequate for the determination of the equilibrium state, whereas Hückel methods exaggerate the steric part and thus larger twist angles are always obtained (71T991; 78T1139). The overestimation of the steric part by EHT methods must be taken into account in the calculated steric barriers. Investigation at the STO-3G Hartree-Fock level was performed on over 30 azabiphenyls constituted by benzene and/or azabenzenes (86IJQ541). Compounds with the same surrounding at the linking bond have very similar conformational behavior, irrespective of the number of nitrogen atoms in non-ortho positions. The equilibrium twist angle was 42.2° for compounds with no nitrogen in an ortho position (a value very similar to the one in biphenyl itself), 33.7° for compounds with one nitrogen, 0° for compounds with two nitrogens in ortho positions on the same ring, 0° for the trans arrangement of compounds with two nitrogens in ortho positions but belonging to two different rings (43.2° for the cis arrangement), 18.2° for compounds having three nitrogens, and 28.2° for compounds with four nitrogens (85MI6; 85T1915; 86IJQ541). The results are given in Table XIV.

Thus, repulsive interactions decrease in the order $C-H\cdots H-C > N:\cdots N \gg N:\cdots H-C$. We wonder if these results reflect only repulsive interactions or if they do also indicate some attractive contribution in the



SCHEME 88

TABLE XIV
 CALCULATED TWIST ANGLE IN POLYAZABIPHENYLS^a

Compound	Dihedral angle	Compound	Dihedral angle
	0		33.7
	0		42.2
	18.2		43.2
	28.2		30–40 (84BCJ341)

^a Taken from (86IJQ541), unless indicated otherwise.

interaction between the lone pair and the hydrogen when possible. In these compounds, the overall torsional barriers, which are quite low, were dissected into conjugative, electrostatic, and steric interactions. These factors could be used in the treatment of compounds with larger steric requirements in ortho positions to identify the conjugation contribution.

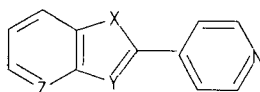
These calculations show that the barriers are quite low in the unsubstituted molecule and little affected by remote substitutions. These compounds provide an interesting basic set for the study of steric barriers when ortho substituents are introduced.

Calculated absorption and magnetic CD spectra were compared with observed spectra to get dihedral angles of 30–40° for the dication of 2,2'- and 4,4'-bipyridyl (84BCJ341). In this work the dihedral angles of 2,2'- and 4,4'-bipyridyl were estimated to be 0 and 30°, respectively.

ii. *Five-membered ring bonded to a six-membered ring.* For a given interring bond length, the interring dihedral angle is expected to be smaller in these systems than in six-membered–six-membered ones due to the

larger internal angles in the five-membered ring. This is generally confirmed by experiment and by calculations.

Extended Hückel MO calculations have been performed on isomeric phenylpyrroles (78T1139), phenylfurans, phenylthiophenes (71T4947), isomeric phenylthiazoles (72T2799), 1-phenylpyrazole (66T2703; 68JCS(B)211; 68JCS(B)725; 70BSF2144; 78T1139), 1-phenyl-1,2,5-triazole, and 1-phenyl-indazole (78T1139). As pointed out earlier, these calculations overestimate the steric contributions and thus exaggerated twist angles are obtained. Calculations show that the barriers are low and an attempt to study the barriers in 2-(4-pyridyl) derivatives **120** (Scheme 89) by low-temperature DNMR was unsuccessful (77H911).



120

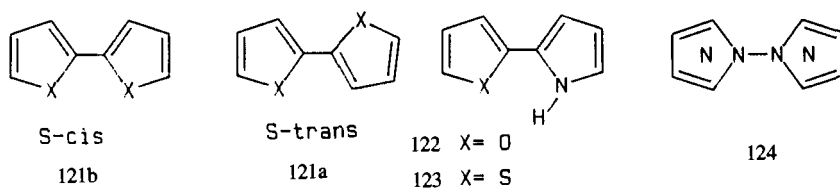
SCHEME 89

The π -barrier in **120** is approximately 16 kJ mol^{-1} , whereas the steric barrier was assumed to be less than 10 kJ mol^{-1} , far too low for DNMR studies.

Substitution in an ortho position increases dramatically the angle of twist, resulting in strong modifications in UV, IR, and NMR spectra. All these techniques were used to estimate the twist angle (66JOC1878; 68JCS(B)211; 73ACS3101; 78MI1; 85OMR259). However, these data do not shed light on the steric barrier, although they are useful diagnostics for the determination of the twist angles.

CNDO/2 calculations on 9-methyl-8-phenyl-6-thiopurine give an angle of twist close to 30° , in agreement with experimental data (74MI3).

iii. *Five-membered ring bonded to a five-membered ring.* Isomeric bifuranyls have been studied by Orti *et al.* (80CPL530; 84JST(108)199; 87JPC545) and isomeric bithienyls by Barone and co-authors (86JCS(P2)907). Theoretical computations (ST0 3G) indicate that all unsubstituted isomeric bifuranyls and bithienyls have planar equilibrium conformations with π -barriers. Slightly nonplanar conformations for 2,2'- and 3,3'-bithienyl have been found by electron diffraction (58ACS1671; 70ACS1389) and NMR studies (74JA1305, 74MI4; 75JCS(P2)154). A mixture of S-trans (78%) and S-cis (22%) rotamers **121a,b** accounts for the experimental liquid-crystal NMR spectroscopy (73JCS(P2)751). The higher π -barrier (maximum conjugation) was estimated by DNMR to be $21 \pm 8 \text{ kJ mol}^{-1}$ (70JA1453; 74JA1305).



SCHEME 90

Fully planar cis and trans conformations with a preference for cis were found for 2-(2-furyl)pyrrole (**122**) and 2-(2-thienyl)pyrrole (**123**) by a combination of dipole-moment studies and *ab-initio* STO-3G calculations (81JCS(P2)127).

In contrast, a series of N–N linked biazoles (**124**) have been found to be more stable at conformations near orthogonality according to LCAO-MO-SCF MNDO method (84CJC687). This particular behavior may be accounted for by the exceptionally short N–N bond and the particularly low conjugative ability of the framework. In the planar transition state, the three main interactions to be considered arise from (1) pairs of hydrogen atoms situated at each ring $C-H \cdots H-C$, (2) pairs of electrons on the nitrogen atoms $N:\cdots:N$, and (3) a hydrogen atom of one ring interacting with a lone pair on a nitrogen of the other ring ($C-H \cdots :N$). A multilinear regression analysis with the whole set of compounds gives a mean value for each interaction, namely $15.4 \text{ kJ. mol}^{-1}$ for $C-H \cdots H-C$, $10.3 \text{ kJ. mol}^{-1}$ for $N:\cdots:N$, and 3.2 kJ. mol^{-1} for $C-H \cdots :N$. This order is similar to that found in six-membered rings (*vide supra*). MNDO calculations give much better agreement with experimental values than those performed by the CNDO/2 approach.

c. Examples of Quantitative Determinations of Steric Barriers.

The previous paragraphs indicate that many heterocyclic rings would be suitable systems for the quantitative determination of steric effects. The DNMR techniques are well documented for rotational processes and in the last few years the tremendous development of chiral phases for high-performance liquid chromatography (HPLC) has simplified the separation of enantiomers and thus the quantitative determination of steric barriers by racemization. However, the experimental determination of steric barriers for planar transition states by DNMR or direct equilibration of enantiomers has not yet received the attention it deserves. We list a number of specific points of interest provided by heterocyclic systems.

1. A great variety of geometrical situations for interacting groups are possible for heterocyclic frameworks associated with a large variety of

conjugation. This gives a source of quantitative data for semiempirical or molecular mechanics calculations.

2. Most heterocycles have a reactivity pattern richer than the corresponding carbocycles. The knowledge of steric requirement will help in the design of reactive functions in chiral surroundings which should find application in asymmetric induction, asymmetric complexation, and asymmetric recognition.

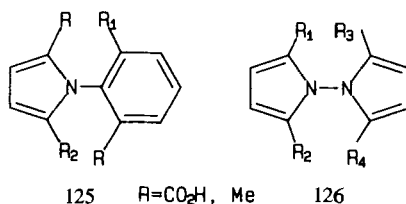
The pioneering work of Adams on the resolution of optically active biphenyls gives the first examples involving heterocyclic analogues: phenylpyrrole **125** and bipyrryl **126** (31JA374; 31JA2353; 31JA3519; 49MI1) (Scheme 91).

The blue-green algae *Rivularia firma Womersley* affords a series of chiral polybrominated biindoles **127a–d**, representative of a small class of natural products which are chiral only because of sterically restricted rotation within the molecule (82JA3628). Symmetric biindole (**127a**) shows no optical activity, although the steric pattern of the $C-sp^2-C-sp^2$ environment appears sufficient to give a rather high barrier to rotation. The total synthesis of some of these biindoles has been achieved in racemic form (84JOC1549; 85JA2943) (Scheme 92).

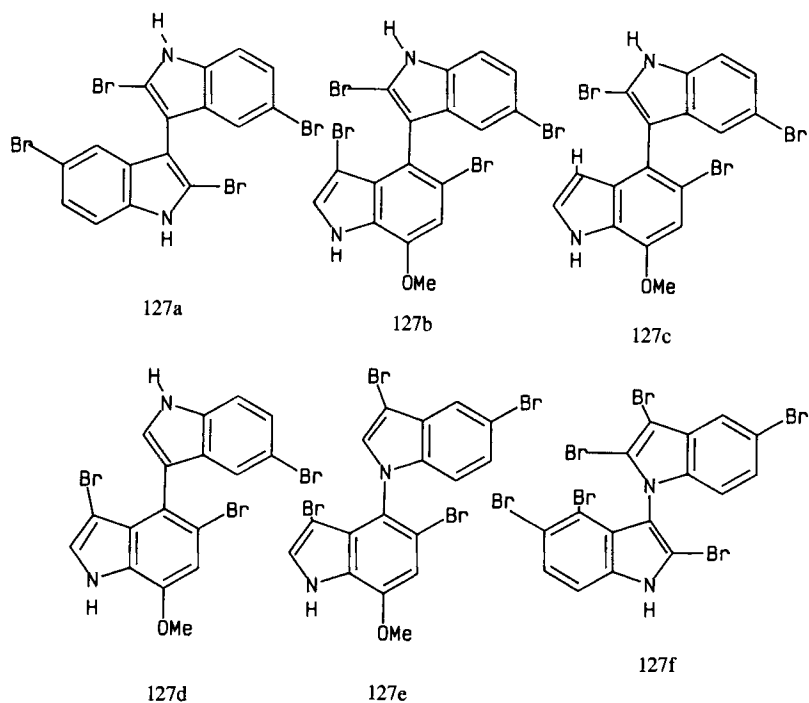
The next examples point out some specificity offered by heterocyclic systems when they replace a phenyl in reference compounds.

4,4'-Dicarboxy-2,2',5,5'-tetraalkyl-3,3'-bithienyls (**128a,b**) were resolved into enantiomers and racemization experiments were carried out in 0.1 *N* sodium hydroxide solution (67AK115). The racemization of the tetramethyl derivative **128a** was 80 times faster than that of the tetraethyl derivative **128b** at 120°C. By comparison, biphenyl analogue **129** shows no racemization after 4 hr at 150°C.

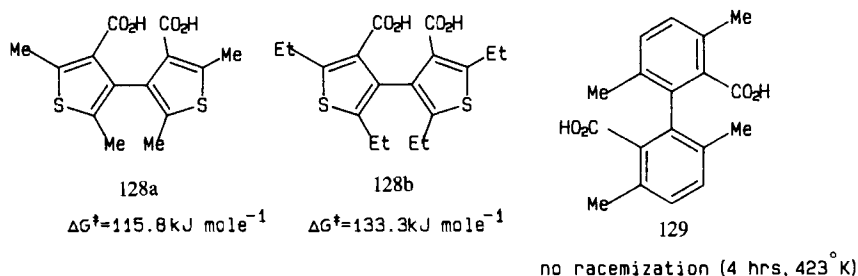
The smaller internal angle in the thiophene as compared to the benzene ring results in larger distances between interacting groups in the transition state as well as reduced buttressing effects and accounts for the observed difference. In these compounds the change in activation energy is mainly enthalpic; negative entropy values were obtained. This is a characteristic of these models in which



SCHEME 91



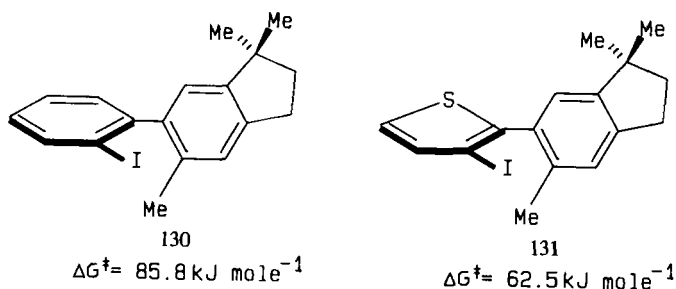
SCHEME 92



SCHEME 93

a hydrogen bonding or easily solvated group is present. More appropriate models are those in which the entropy of activation is close to zero. The same trend for the replacement of a phenyl by a thiophene is observed in iodo compounds **130** and **131** (80JA5618) (Scheme 94).

Various 3,3'-bithienyls and one 3,3'-biseleniyl with substituents in the 2,2'- and 5,5'-positions have been studied by X-ray and CD methods and their

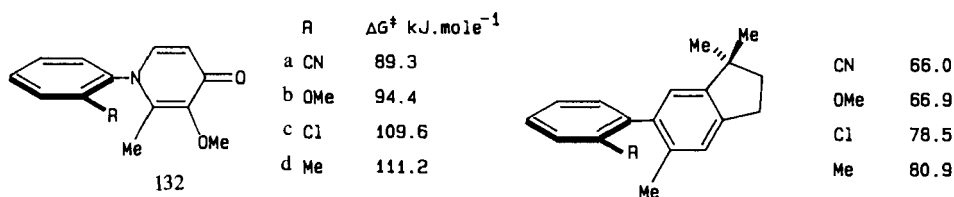


SCHEME 94

properties compared with those in the corresponding biphenyls (75CS131; 75CS173; 75CS204; 76CS66). By DNMR, it was possible to determine the barrier to rotation in a number of bridged 3,3'-bithienyls with blocking substituents in the 2,2'- or 4,4'-positions. The barriers are lower than in the biphenyl analogues (74CS226; 76CS117; 76CS120).

A clear example of interring bond length effects on the barrier is provided by a comparison of data obtained in *N*-aryl-4-pyridones **132a–d** compared to the homologous biphenyls. The shortening of the linking bond is associated with a buttressing effect of the MeO group and gives barriers to rotation roughly 30 kJ mol^{-1} higher in the former series, for the same steric surroundings (85T229). The resulting barriers are high enough to allow the total or partial resolution of enantiomers of **132a–d** by liquid chromatography on triacetylcellulose, a technique which should greatly improve the number of studies in this field (85MI3).

In the previous examples, the transition state for enantiomerization is well defined, in it the substituents on each ring are interacting with one hydrogen on the other. The second possible transition state, in which the two substituents are on the same side, is too high in energy to contribute to the enantiomerization path. The situation is different when two substituents are situated on the same ring in front of an ortho–ortho' unsubstituted ring. The two isomeric transition states are very close in energy since the possible differences arise from a remote effect of substituents in noninteracting

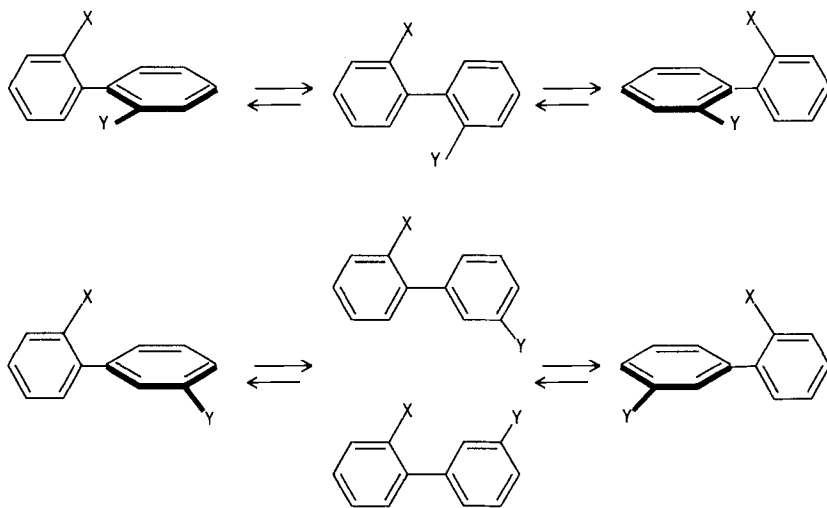


SCHEME 95

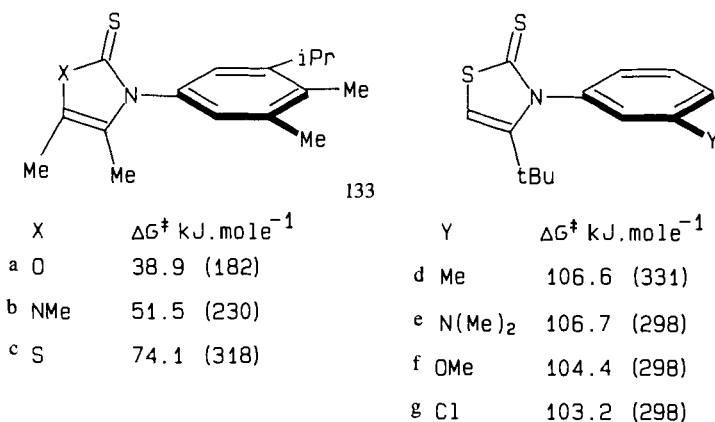
positions (dipole–dipole interactions, buttressing effect on nitrogen, solvent effect). The occurrence of more than one transition state must be taken into account in the given barriers. For two transition states, the maximum uncertainty range is $RT \ln 2$, which is acceptable for large barrier variations but may be large enough to hamper the determination of subtle effects (Scheme 96).

N-Arylazolinethiones **133a–c** may have two almost equivalent planar transition states, the populations of which should not be changed too much by variation of the annular heteroatom (Scheme 97). Thus the barriers to rotation around the N—C bond were determined by DNMR using the prochiral isopropyl group as a probe (85JCS(P2)273). The barriers are dramatically affected by the nature of the heteroatom X in the ring. The largest barrier is obtained for the thiazolinethione (X = S). The changes were accounted for by the geometric difference induced by the modification in X, although some modifications in the conjugative ability of the heterocycle are certainly involved (Scheme 97).

These examples illustrate the almost unlimited geometrical possibilities which may be encountered in heterocyclic systems. They are useful in the design of steric requirements of substituents that allow separation into stable enantiomers. This was achieved by considering that **133c** exhibits a barrier similar to the one found in 2,2'-dimethylbiphenyl, in which replacement of a methyl group by a *t*-butyl results in a barrier increase of $\sim 32 \text{ kJ. mol}^{-1}$. Thiazolinethiones with a *t*-butyl group in position-4 (**133d–g**) were resolved



SCHEME 96

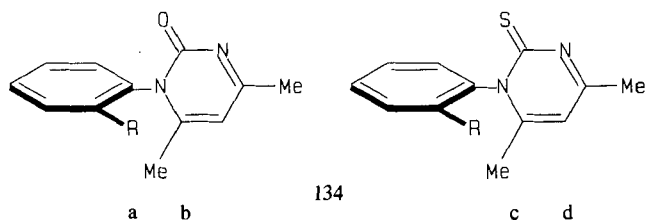


SCHEME 97

on triacetylcellulose (86NJC399). Electron-accepting substituents slightly decrease the barriers, since the thiazoline-2-thione is electron donating towards the aryl ring but owing to the limited range of energy variation and the uncertainties associated with the possible changes in transition state populations the discussion must be qualitative. Solvent effects are limited but significant; solvents of low polarity decrease the barrier to rotation. Further substitution in the ortho position of the aryl ring gives a series of permanently chiral compounds which cannot be racemized without decomposition (86UP2).

4,6-Dimethyl-1-(aryl)pyrimidine-2(1*H*)-(thio)ones (**134a-d**) were resolved into enantiomers with D-camphor-10-sulfonic acid and their barriers to racemization determined by polarimetry (80JCS(P1)1599). These barriers deserve comment, since their trend is opposite to what is expected (Scheme 98).

A lower barrier is found on going from the C = O to the C = S derivatives and the authors proposed the intervention of greater single-bond character of the thione. This would probably promote bond bending, leading to a smaller steric requirement of the thiocarbonyl group compared to the carbonyl. This



SCHEME 98. a, R = Me; b, R = Cl; c, R = Me; d, R = Et

is in marked contrast with the effect observed for the same structural modification when isopropyl group rotations in thiazoline-2-one and -2-thione are considered (85ACR80). Furthermore, there is apparently no buttressing effect of the chlorine atom in a meta position. In fact, the reported barrier is 3 kJ mol⁻¹ lower. One has to expect a net increase of 10–15 kJ mol⁻¹ due to such a perturbation by analogy with biphenyl analogues (80JA5618). We believe more experimental studies will be worthwhile.

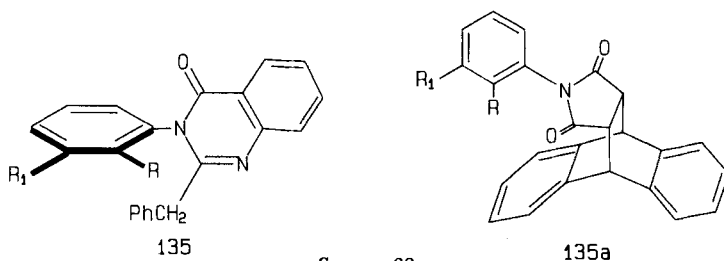
The barriers to rotation about the aryl C—N bonds were determined by DNMR in 3-aryl-2-benzyl-4(3*H*)-quinazolinones **135** (72TL5239; 75CJC3431) and in imide **135a** (76AJC295) (Scheme 99).

The presence of an ortho substituent on the aryl ring gives rise to such a high barrier that it was not overcome by DNMR and resolution seems possible. Ortho-unsubstituted compounds give barriers ranging between 82.7 and 99 kJ mol⁻¹, depending on the substitution in the meta position in **135**. They have not been corrected for the intervention of two possible transition states. These barriers are larger than those obtained in thiazoline-2-thione (**133c**) as a balance of the interaction on going from thione to carbonyl group and from a five-membered to a six-membered ring.

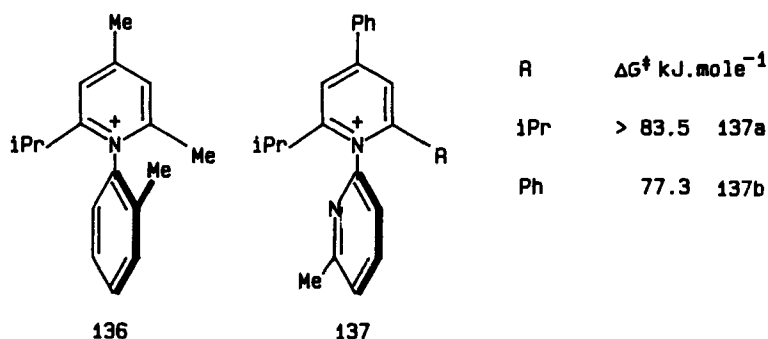
A particularly interesting access to heterocyclic analogues of biphenyl is given by the reaction of pyrylium salts with primary amino compounds. Atropoisomerism was detected by nonequivalence of the methyls of the isopropyl group in **136** (76RRC251; 82AHC(Suppl 2)1). These compounds should have rotational barriers larger than those of the biphenyl analogue due to the shortening of the interring bond. The barriers have been determined for pyridylpyridinium salts **137a,b** 83OMR587 (Scheme 100).

All these previous examples are illustrative of the geometrical possibilities offered by heterocyclic compounds. When the heterocyclic framework is not directly involved in the interacting groups, results similar to those found in carbocyclic analogues are obtained. Thus, similar barriers are observed in isomeric biazanaphthyl and binaphthyl since the geometrical variation is minimal (52JCS4133; 54JCS3464; 80JA5618).

We have already underlined one advantage of the heterocyclic framework compared to carbocyclic analogues: to provide reactive functions in a chiral



SCHEME 99



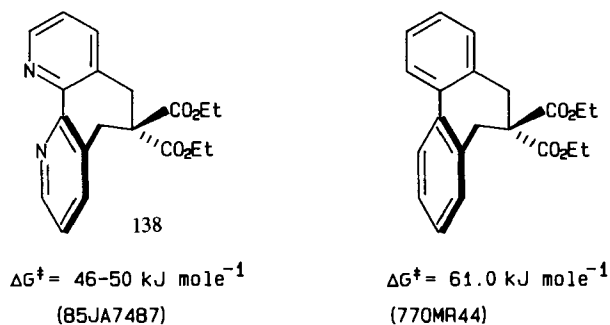
SCHEME 100

environment. The work of Rebek *et al.* is particularly illustrative (78JA4315; 79JA4333; 80TL2379; 85JA7481; 85JA7487).

These authors have studied the effect of complexation on dynamic processes in bridged bipyridyl derivatives (**138**) (Scheme 101).

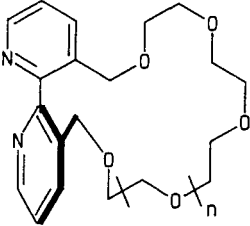
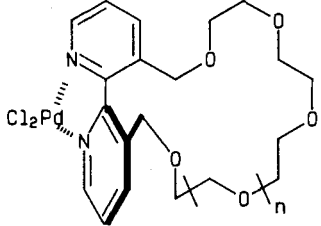
In these compounds the transition state to rotation is more or less planar whereas the ground state is twisted, but in contrast to unbridged bipyridyl the transition state is the one in which the two nitrogen atoms will pass "in front." Complexation by a metal or hydrogen bonding stabilizes the planar transition state. The lowering of the barrier for racemization is at least 33.5 kJ mol^{-1} with complexation with PdCl_2 . The results are summarized in Table XV.

This concept is applicable to many heterocycles with the suitable functional pattern. 3,3'-Annulated 2,2'-bipyridines and analogues have been studied by Thummel and co-workers (84JOC2208; 85JOC666; 85JOC3824). The basicity and ultraviolet absorption spectra may be related to the dihedral angle between the rings, which is governed by the length of the bridge. The twist angle between the two pyridine rings in 2,2'-dipyridinium-bridged diquaternary salts can be estimated as well from spectroscopic data (75CB1682;



SCHEME 101

TABLE XV
SELECTED EXAMPLES OF THE EFFECT OF COMPLEXATION ON BARRIERS TO ROTATION IN
BIPYRIDYLS

Compound	<i>n</i>	ΔG^\ddagger (kJ mol ⁻¹)	Compound	<i>n</i>	ΔG^\ddagger (kJ mol ⁻¹)
	0	> 107		0	61.0
	1	> 107		1	58.5
	2	> 107		2	58.1

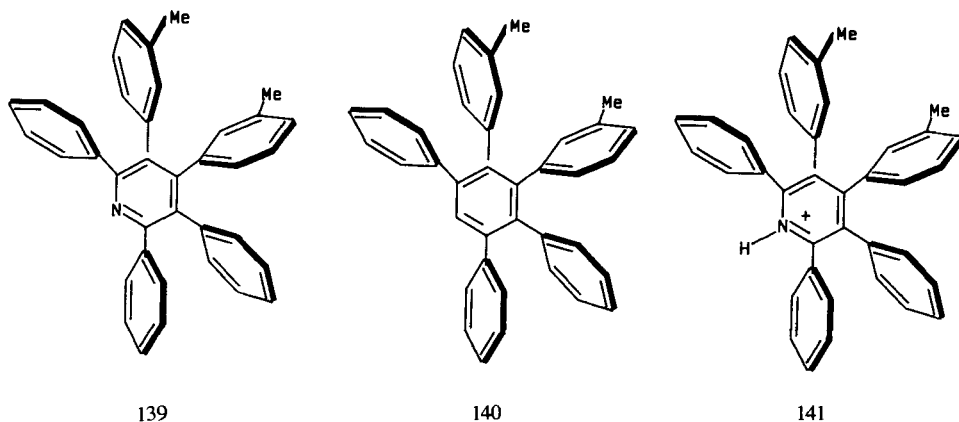
87JOC521). The barrier to enantiomerization in the propane-bridged salt is 69 kJ mol^{-1} (87JOC521).

The next section reports some miscellaneous examples of high barrier to rotation around an sp^2-sp^2 -bond and emphasizes the possible applications.

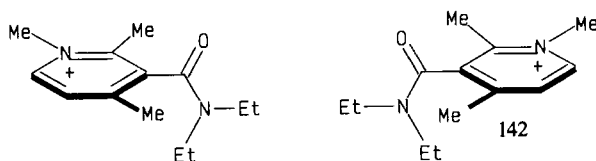
Restricted rotation in pentaarylpyridine **139** was used to determine the steric requirement of the nitrogen lone pair by comparison with the corresponding pentaarylbenzene(**140**) (80JOC2511). The variable-temperature NMR results show that in **139** the nitrogen lone pair has a smaller steric requirement than does hydrogen in the pyridinium analogue (**141**) (Scheme 102).

Atropoisomers of *meso-o*-tolylporphinatonicel(II) were studied by DNMR and the barriers to rotation estimated to be higher than 108 kJ mol^{-1} (71TL4949). Atropoisomers of *meso-o*-hydroxyphenylporphyrin analogues were separated by thin-layer chromatography into four components (69TL3071). Application of these twisted forms were found in the design of a "capped" porphyrin, such as [5,10,15,20-[pyrromellitoyltetrakis(*o*-(oxyethoxy)phenyl)]porphyrinato]chloroiron(III) in which the four oxyethoxy groups are directed on the same side of the porphyrin framework (82JA3715). Rotational barriers in ortho-substituted tetraarylporphyrins have been reported for various substituents: halogen (87JA341), hydroxy and methoxy (69TL3071; 79JOC2551), cyano (81BCJ3518), and amino derivatives (81JA1226; 83JPC3918).

In a field closely related to biphenyl, hindered rotation around the pyridyl-amide bond allowed the resolution of the nicotinamide analogue **142** into enantiomers. Compound **142** was optically stable at 25°C in water; at higher temperatures racemization occurs (e.g., $t_{1/2} = 3.1 \text{ hr}$ at 100°C) (82RTC191;



SCHEME 102



SCHEME 103

86CC536). Application of these results to model the role of the CONH_2 group in redox coenzyme $\text{NAD(P)} + / \text{NAD(P)H}$ seems promising (86CC536) (Scheme 103).

IV. Relations between Intra- and Intermolecular Steric Effects

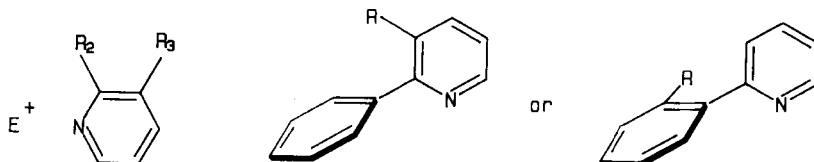
In Section II, devoted to intermolecular processes, it appeared that most of the quantitative analysis of steric effects was made using a single parameter approach. However, analysis has shown that a correct description of the size of a substituent rests on its preferred conformational states, which are related to the interactions with both the planar heteroaromatic ring to which it is bonded and neighboring groups. This was the topic of Section III.

Section IV correlates intramolecular and intermolecular steric effects where it is important to consider the ease of strain energy minimization in the order rotation > bending > stretching, and also the three major structural situations discussed below in Sections IVA–C.

A. ADJACENT GROUP INTERACTIONS

The mode of interaction of a substituent R_2 ortho to a reactive center (nitrogen atom in the given example) and adjacent to a substituent R_3 depends mostly on the symmetry of R_2 (Scheme 104).

When R_2 is spherical with C_∞ symmetry, the preferred mode of energy minimization will be bond bending as in the hindered rotation of biphenyls.



SCHEME 104

SCHEME 105

The term *buttressing effect* was then introduced (50JA19). In rotation barriers of biphenyls or azabiphenyls, this usually increases the rotational barrier, this corresponding, in intermolecular processes, to a reaction rate decrease. However, when R_2 strongly modifies the electronic effect of R_3 by steric inhibition of resonance, this rate decrease can be tempered or enhanced. When R_2 is planar, the major mode of energy minimization is rotation as discussed for $sp^2 - sp^2$ -bonds. In all cases, whatever the symmetry of R_3 , this results in a large decrease of steric hindrance toward the reactive nitrogen and, in general inplane reactivity.

The apparent size of a planar group can be reduced by rotation induced by R_3 and also by ortho substituent R_2 (Scheme 105).

This is clearly exemplified by the respective S^0 values of R_2 groups such as phenyl (-1.82), 2-tolyl (-0.77), 1-naphthyl (-0.75), mesityl (-0.23), and 2-pyridyl (-2.35) and 2-thienyl (-2.46) (80JCS(P2)1350).

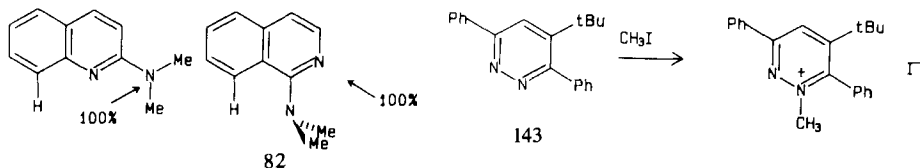
Another example is given by the dramatic change in the regioselectivity of the quaternization reaction of 2-dimethylaminoquinoline compared to 1-dimethylaminoisoquinoline. It was quoted (85MI5) that "rather strangely, 1-dimethylaminoisoquinoline **82** undergoes methylation at the annular nitrogen which is the most sterically hindered of all these nitrogen atoms." This is not unexpected, because the dimethylamino group is twisted as in **82**, providing a larger accessibility to the nitrogen atom (Scheme 106).

A similar explanation was given (67ACS1067) for the exclusive methylation at the N-2 nitrogen atom in pyridazine **143**, the phenyl group at C-3 not being coplanar with the pyridazine ring (Scheme 106).

Such induced conformational changes influence the rates of dealkylation. Examples will be given in the section on dealkylation.

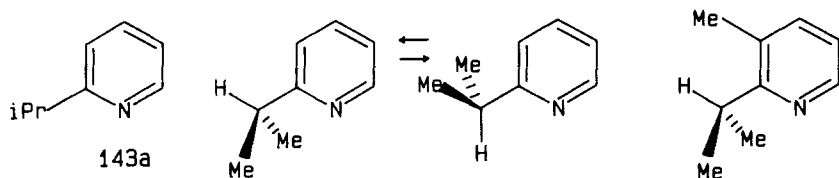
Clearly, however, this induced conformational change will, by contrast, dramatically decrease the accessibility of the π -system of the heterocycle and thus addition reactions at a bridge head atom will be considerably hindered.

When R_2 is a tetrahedral substituent, the situation is more diverse but can be analyzed simply. In Section II, the steric effect of an alkyl group was analyzed by the quaternization reactions of 2-alkylpyridines. The conformational state of an isopropyl group attached to a planar framework was depicted in Section III.

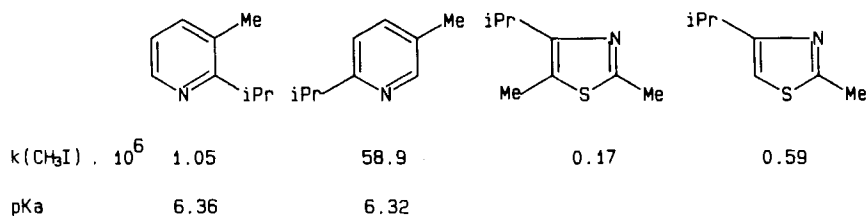


SCHEME 106

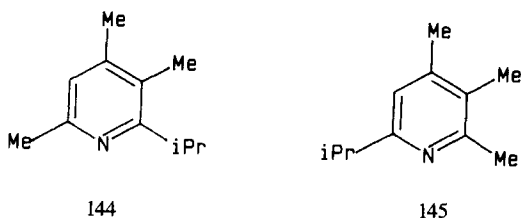
In 2-isopropylpyridine (**143a**), the isopropyl group adopts two opposite conformations: one in which the bulky face is directed toward the reactive nitrogen and one in which one hydrogen is pointing into the plane (Scheme 107). These two conformations exhibit very different steric requirements toward the incoming quaternizing methyl group. Introduction of a methyl group in the 3-position increases the population of the hindered conformer A and prevents rotation of the isopropyl in the transition state.



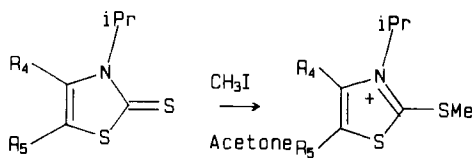
SCHEME 107



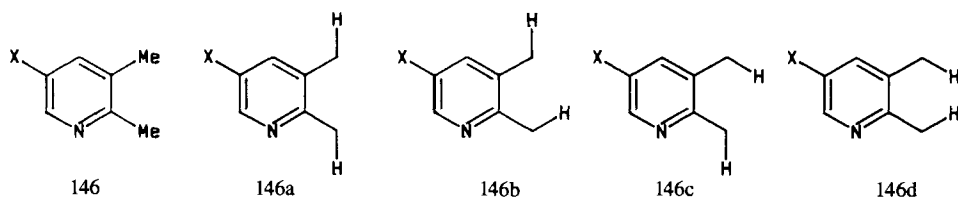
SCHEME 108



SCHEME 109



SCHEME 110



SCHEME 111

This was clearly exemplified by the kinetics of alkylation by methyl iodide in nitrobenzene (72MI2). The conformational aspects of such a steric retardation also was confirmed in the azole series (73JA3807) (Scheme 108).

A similar effect was observed when the electrophile was a lanthanide reagent reacting with isomeric pyridines **144** and **145** (85TL4669, 85TL4673) (Scheme 109).

In thiazoline-2-thiones, a correlation was found between the conformational state of the 3-isopropyl group and the rate constant for alkylation by methyl iodide at sulfur (Scheme 110).

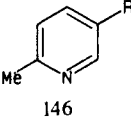
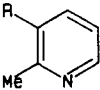
The larger the population in which the bulky face of the isopropyl group is directed toward the sulfur, the larger is the strain release in the transition state during alkylation (74JCS(P2)1304; 76JA2847).

The remote steric effect of an alkyl substituent adjacent to a methyl group in an ortho position of a reactive nitrogen such as in 2-methylpyridine (**146**) was analyzed in terms of a *buttressing effect* (56JA5375; 72MI2; 81JA5982). However, in an analysis of the rate of alkylation by methyl iodide of polymethylpyridines, the induced "gear-clashed" conformation was responsible for the small steric retardation of the reaction rate in 2,3-dimethylpyridine and an analogue (83T4209). MINDO/3 calculations (84T3971) also confirmed that the "gear-clashed" conformation A was more stable than B, C, or D (Scheme 111). In conformation A (Scheme 111), the "pointing" hydrogen is similar from a steric point of view to a peri hydrogen in quinoline and, nicely, the same steric size was found in a quaternization reaction (83T4209).

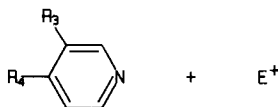
Angle bending also occurs in addition to conformational effects in the case of severe interactions such as in 3-*t*-Bu-2-Me-pyridine (**147d**) (Scheme 112) (72MI2) or in pentamethylpyridine (83T4209).

B. REMOTE STERIC EFFECTS ON REACTION RATES

In this case, there is no direct steric effect between the adjacent substituents (Scheme 113) and the incoming reagent and the changes in reactivity induced

	R =	Me	Et	iPr	tBu
 146	pK _a =	6.42	6.45	6.50	6.60
	k _{CH₃I} =	37.6	36.2	40.3	43.7
 147	pK _a =	6.56	6.59	6.63	6.81
	k _{CH₃I} =	19.4	16.4	17.4	11.2

SCHEME 112



SCHEME 113

by SSE will come from electronic perturbations or from geometrical changes of the molecular backbone.

The importance of the SSE will depend mostly on the symmetry of the substituents, with rotation being the less energetic molecular motion in energy minimization. The largest changes caused by SSE at small steric interactions will be due to substituents having a large σ_R constant much dependent on conformations, namely NMe₂ ($\sigma_R = -0.50$). Other groups having smaller σ_R values (NO₂, Ph, COR, CO₂R) or being less or not conformationally dependent (OR, Cl, Br) will be less affected. The SSE with NR₂ or NO₂ groups, also termed steric inhibition of resonance (SIR), can be detected not only by changes in reactivity, but also by changes in pK_a, since in both cases there is no steric effect ortho to the reactive center. Typically, the values in Table XVI show that a methyl ortho to a NMe₂ prevents coplanarity of the NMe₂ and reduces strongly (~ 1.45 pK_a unit) the resonance donor effect of the NMe₂ group (61JCS3939).

TABLE XVI
pK_a VALUES OF SUBSTITUTED PYRIDINIUM IONS

R ₃	R ₄	pK _a
H	H	5.19
Me	H	5.60
H	NMe ₂	9.71
Me	NMe ₂	8.68

TABLE XVII
PIPERIDINE DECHLORINATION RELATIVE RATE CONSTANTS

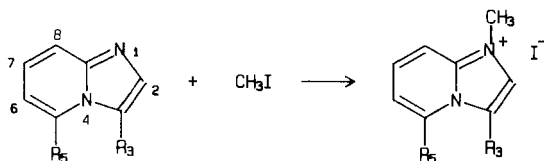
Nitro compound	Aza-aromatic	Relative rate (NO ₂ /aza)
		6.5
		0.6

A similar behavior in a different reaction (Table XVII) shows that when the coplanarity of a NO₂ group is prevented in an S_NAr reaction, the activating power of the nitro group, due in part to its resonance accepting effect ($\sigma_R = +0.15$), can become less than that of a ring nitrogen (54JCS1190).

Angle bending is the next step in energy minimization. It occurs when strain release by rotation of substituents is not enough to accommodate all the steric strain or when rotation is not possible, as with spherical substituents. Quantitative results are scarce; an interesting example is the methylation of a series of 3,5-dialkylimidazo(1,2-*a*)pyridines (81T83; 81T91) (Scheme 114).

The introduction of a methyl substituent in position-3, -5, -6, -7, or -2 has a rate-accelerating effect of, respectively, 1.83, 1.29, 1.42, 2.05, and 1.13. There is a rate-decreasing effect of 5.25 when the methyl is introduced in position-8. This is in line with the effect of substituents in five-membered rings and benzo analogues. The influence of two substituents of increasing size is additive in positions-3,6 and -3,7, but in contrast substituents in positions-3,5 induce a kinetic nonadditivity, $S = k/k_{\text{cal}}$ (Table XVIII). The nonadditivity term S has been correlated with the variation of ϕ , the angle N-1—C-9=C-8 (Scheme 115), estimated by complete geometry optimization using the MINDO/3 algorithm (84JA143). The correlation is

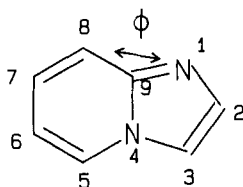
$$S = -8.01 \cos \phi - 2.77 \quad (r = 0.971)$$



SCHEME 114

TABLE XVIII
QUATERNIZATION OF IMIDAZO(1,2-*a*) PYRIDINE

R_3	R_5	k	k_{cal}	$S = k/k_{cal}$	$\phi = \text{angle N-1-C-9-C-5}$
Me	Me	1.87	2.00	0.93	130.4
Et	Me	1.90	2.10	0.90	130.2
<i>i</i> Pr	Me	1.76	2.16	0.81	129.8
<i>i</i> Pr	Et	1.70	2.35	0.72	129.1
<i>i</i> Pr	<i>i</i> Pr	1.75	2.52	0.69	128.2



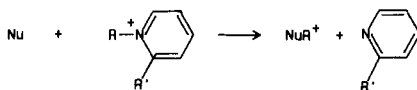
SCHEME 115

C. DEQUATERNIZATIONS

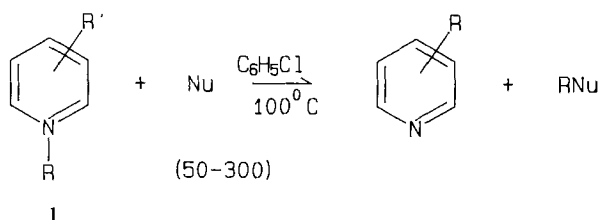
Now the pyridine derivative behaves as a leaving group (Scheme 116) and the steric strain existing in the pyridinium ion is released during the reaction, resulting in a steric acceleration (81JOC3823). This is part of a two-step procedure for converting primary amines to other functionalities, developed by A. R. Katritzky and his group (80T679; 84AG(E)420).

The first step involves the formation of a pyridinium ion by reaction of a pyrylium ion with a primary amine; the second step (dequaternization) has been studied more extensively than the first (amine + pyrylium). This important work on dequaternization deserves special mention because, besides the value for synthesis and understanding of steric acceleration, it sheds new light on the mechanism of aliphatic nucleophilic substitution (84CSR47).

The results of the kinetic studies have been summarized (85H1765); they are usually conducted in chlorobenzene at 100°C under pseudo-unimolecular conditions (Scheme 117).



SCHEME 116



SCHEME 117

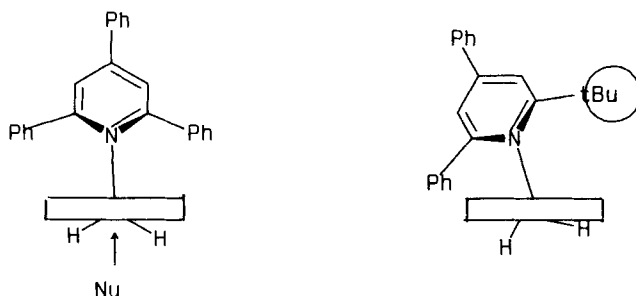
When R is primary alkyl, the second-order rate constant k_2 is obtained by taking the slope of k_{obs} vs. concentration of the nucleophile. The plot passes through the origin, indicating a pure S_N2 mechanism without S_N1 participation. The reference pyridinium ion is the 2,4,6-triphenyl derivative (because pyrylium precursors with phenyl substituents are more easily prepared) (82AHC(Suppl 2)1) but numerous other substituents have been introduced into the ring. Rate constant values reported in Table XIX, where release of steric strain has a major influence, are in agreement with the role of structural factors discussed in Section IV,A.

Successive introduction of phenyl groups into positions-2 and -6 (entries 1–3 of Table XIX) increases the rate by factors of 3.4 and 5.3, respectively. An

TABLE XIX
RATE CONSTANTS FOR THE REACTION OF SCHEME 117

Entry	R ₂	R ₃	R ₄	R ₆	k_2^a	Reference
1	Ph	H	H	H	0.27	83JCS(P2)1421
2	Ph	H	Ph	H	0.93	
3	Ph	H	Ph	Ph	4.94	81JOC3820 80TL2697
4	2-Pyridyl	H	Ph	Ph	18.0	82JCS(P2)1041
5	2-Thienyl	H	Ph	Ph	8.19	
6	2-Thienyl	H	Ph	2-Thienyl	19.19	
7	Benzimidazol-2-yl	H	Ph	2-Thienyl	43.5	
8	Benzothiazol-2-yl	H	Ph	Ph	31.6	
9	Ph	Me	Ph	Ph	0.8	81JOC3823
10	Ph	Ph	Ph	Ph	1.6	80TL2701
11	Ph	H	—MeC ₆ H ₄	Ph	3.16	82JCS(P2)1041
12	Ph	H	ClC ₆ H ₄	Ph	6.89	
13	Ph	H	<i>m</i> -ClC ₆ H ₄	Ph	6.74	
14	Ph	H	<i>m</i> -O ₂ NC ₆ H ₄	Ph	9.06	
15	<i>t</i> -Butyl	H	Ph	pH	1.07	81JOC3823 80TL2701

^a Second-order rate constant, $k_2 \times 10^3 \text{ mol liter}^{-1}$.

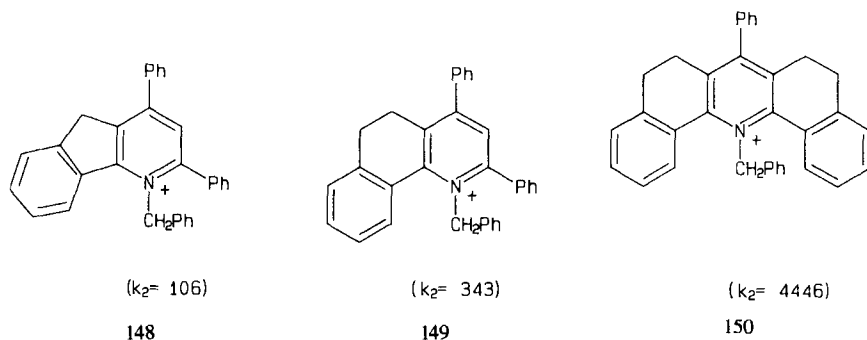


SCHEME 118

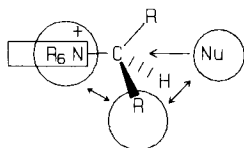
ortho heterocyclic group in position-2, instead of a phenyl, also increases the rate, due to a better coplanarity (entries 4–8), as already found in S^0 values. A methyl or a phenyl in position-3 rotates the 2-phenyl and reduces the rate (entries 9, 10). Substituents para to the 4-phenyl group have little effect. Electron-donating groups increase the basicity of the pyridine and reduce its leaving ability (76JOC2621); electron-withdrawing groups have the opposite effect. A *t*-butyl group in position-2 induces a small increase in rate (entry 15), even though its S^0 parameter is much larger than that of a phenyl, probably due to the fact that a bulky sp^3 -hybridized substituent makes a less symmetrical TS and prevents the overlapping of $2p_z$ orbitals (Scheme 118).

In agreement with this hypothesis, the steric hindrance to solvation, estimated from the difference in measured and “additive” pK_a values (Δ) is greater for 2-*t*-butyl-4,6-diphenyl than for 2,4,6-triphenylpyridine, indicating an expected larger steric effect in the former (83JCS(P2)45). The best result is obtained with benzothiazol-2-yl, which tends to have a big steric effect in the plane of the pyridinium (entry 8) (Scheme 119).

Other pyridinium ions have been prepared with coplanar groups, such as the indeno derivative **148** ($k_2 = 106$), the dihydronaphtho derivative **149**



SCHEME 119



SCHEME 120

($k_2 = 343$), and the bis(dihydronaphtho) derivative **150** ($k_2 = 4450$), which gives, so far, the highest rate constant (81JOC3823). The order of reactivity based on the 1-substituent is comparable to that observed in substitution at the sp^3 -carbon: benzyl > alkyl > methyl > primary alkyl > secondary alkyl. Neopentyl and secondary alkyl are more reactive than usual (83JCS(P2)1427), probably because in normal S_N2 substitution at an sp^3 -carbon they prevent the approach of the incoming nucleophile, whereas in an S_N2 reaction with bulky leaving pyridines they also increase the strain in the ground state and thereby accelerate by strain release (Scheme 120).

With the isopropyl substituent on nitrogen, the kinetic plot (Fig. 10) reveals an S_N1 contribution to the rate constant (80TL2697).

All the secondary alkyl derivatives show also a clear first-order component. The kinetic border between S_N2 and S_N1 depends on chemical and on physical parameters. For example, all benzyl substituents on nitrogen undergo an S_N2

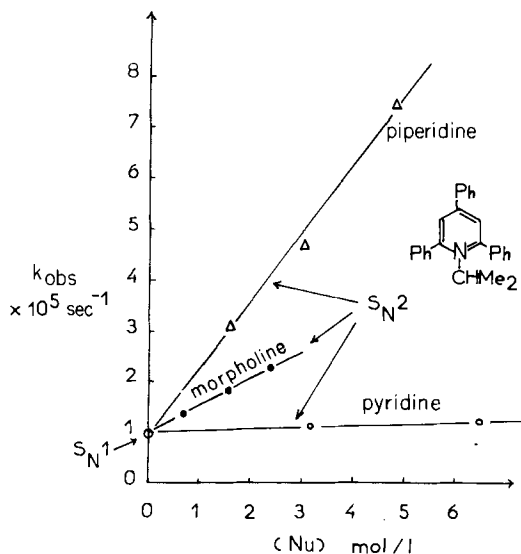
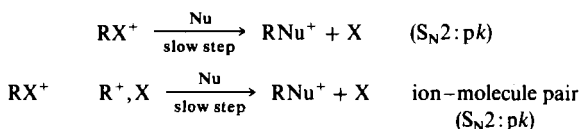


FIG. 10. Simultaneous S_N1 and S_N2 contributions to nucleophilic substitution, evidenced by kinetic plot.

reaction, except *p*-methoxybenzyl, which gives S_N2 and S_N1 (81JOC3831; 82JCS(P2)1055); 1-phenethyl-2,6-diisopropyl-4-phenylpyridinium ion reacts with piperidine by an S_N2 path at 60°C and mainly by S_N1 at 100°C (81JOC3831).

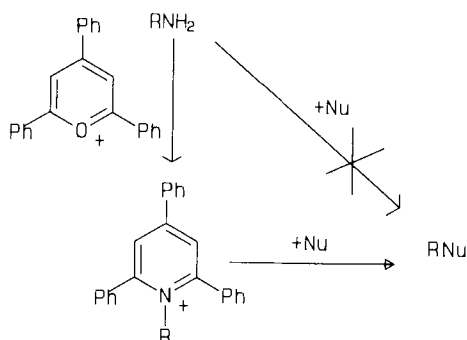
Moreover, the simple S_N1/S_N2 dichotomy is complicated by reaction via an intimate molecule ion pair, as shown by product analysis of secondary 2-pentyl and 3-pentyl substrates (84JCS(P2)349). When the carbocation, in an intimate ion molecule pair, has time to equilibrate, a 50/50 ratio of 3- and 2-pentyl product is obtained. When the nucleophile is reactive enough (like morpholine), the cation of the intimate ion molecule pair is trapped before rearranging and the *N*-(2-pentyl) derivative gives a 2-pentylmorpholine while the *N*-(3-pentyl) derivative gives a 3-pentylmorpholine (84JCS(P2)349). Rate constant variations, under high pressure, have been used to distinguish between a simple S_N2 , where the rate constant increases at higher pressure ($V < 0$), and an S_N2 on an intimate ion-molecule pair, which involves a preequilibrium and shows a rate constant decrease at higher pressure (84JA1879).



In addition, the transfer of *N*-substituents from pyridinium cations to nitroalkane anions involves an electron-transfer mechanism not of the normal radical chain variety (83JA90). Further studies delineating the boundaries of competitive, distinct pathways in these reactions would be of general interest for better understanding of nucleophilic substitutions (86CJC1161, 86JA7295; 87ACR(ip)).

V. General Applications in Synthesis

We shall consider methods or reagents of general interest in synthesis, in which steric effects have been associated with heteroaromatics, rather than the mechanistic examples of reactivity and selectivity changes induced by steric effects which have been reported above. Dequaternization of pyridinium salts, discussed in Section IV,C from the point of view of mechanisms, is a general method for converting primary amines to other functional groups (80T679) (Scheme 121).

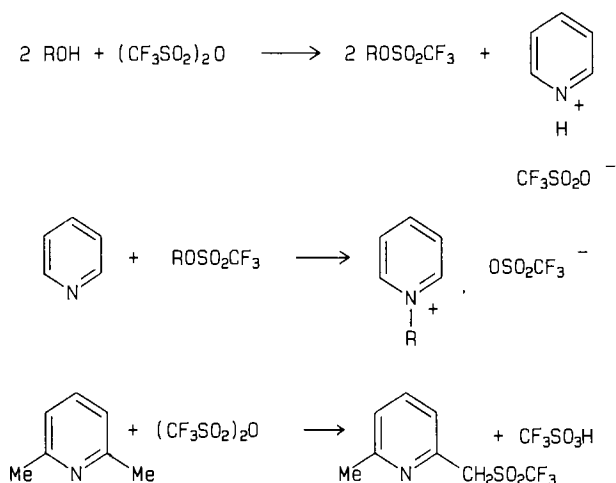


SCHEME 121

2,4,6-Triphenylpyridinium ion is easily obtained by stirring the pyrylium salt with a 10% excess of the amine at 20°C in ether or dichloromethane (80T679). Pyridinium salts react at much higher temperature, depending on the nature of the nucleophile, and several improved procedures have been devised. In summary, primary amines can be converted to the corresponding halides: iodides (79JCS(P1)433), bromides (79JCS(P1)436), chlorides (79S437), and fluorides (79CC238). Oxygen and sulfur nucleophiles are used to obtain esters and alcohols (77CC701), ethers (79JCS(P1)418), aldehydes (79JCS(P1)2500), thiocyanates (78CC133; 79JCS(P1)1953), and thiols via thiuronium ion. Nitrogen and phosphorus nucleophiles afford N-substituted succinimides, phthalimides, benzenesulfonamides, tertiary amines, and azides. Reactions with carbon nucleophiles give C-benzylated malonate, cyanoacetate, phenylacetate (80T679), and C-alkylated nitro compounds (79CC602). Primary alkyl- and arylamines are converted into the corresponding hydrocarbons (79CC300).

2,6-Di-*t*-butylpyridine (2,6-DTBP) and the 4-methyl derivative are of special interest in catalysis because they are basic and nonnucleophilic. Typical examples of their use are found in the synthesis of esters of trifluoromethane sulfonic (triflic) acid. A less hindered pyridine, when added to the reaction medium, serves to neutralize the triflic acid formed (82S85); however, a consecutive alkylation reaction of pyridine with the alkyl triflate occurs. This can be avoided using a more hindered base such as 2,6-dimethylpyridine. But in this case another side reaction takes place, giving mostly a trifluoromethylsulfinyloxymethylpyridine (83JOC1776). The use of 4-methyl-2,6-di-*t*-butylpyridine (76JOC3034) prevents both side reactions (83JOC1776) (Scheme 122).

The sterically hindered 4-methyl-2,6-di-*t*-butylpyridine (MDTBP) has been used to elucidate the mechanism of carbocationic polymerization (80MI3),



SCHEME 122

and to control the structure of macromolecules. Kennedy and Chou (79MI1; 82MI3) suggest that the precise tailoring of polymer molecules by cationic methods may be achieved if undesirable proton transfer reactions giving uncontrolled initiation or chain transfer to monomer are avoided. In agreement with this hypothesis, several sterically hindered amines, in particular 2,6-DTBP, give improved results in terms of yield, molecular weight, and molecular weight distribution (82MI3, 82MI4).

VI. Conclusion

There has been a decisive evolution in the treatment of steric effects in heteroaromatic chemistry. The quantitative estimation of the role of steric strain in reactivity was first made mostly with the help of linear free energy relationships. This method remains easy and helpful, but the basic observation is that the description of a substituent by only one parameter, whatever its empirical or geometrical origin, will describe the total bulk of the substituent and not its conformationally dependent shape. A better knowledge of static and dynamic stereochemistry has helped greatly in understanding not only intramolecular but also intermolecular steric effects associated with rates and equilibria. Quantum and molecular mechanics calculations will certainly be used in the future to a greater extent.

Heteroaromatics have features in common with aromatic hydrocarbons. But the variety of geometrical situations, the number of heteroatoms and their

associated reactivity, and the ease of monitoring stereochemistry often associated with the presence of heteroatoms all have made, and will continue to make, heterocycles exceptional probes for better understanding of reactivity, structures, and the relations between them.

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Reactions of Azines with Bifunctional Nucleophiles: Cyclizations and Ring Transformations

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I. Introduction

Nucleophilic reactions are synthetically very useful in the chemistry of nitrogen-containing six-membered aromatics. This field has been extensively studied and well documented in the literature (64AHC285; 65AHC145; 68MI1; 73KGS723; KGS1155; 73MI1; 73UK1415; 74KGS3; 76RCR454; 76UK908; 78ACR462; 78H33; 78KGS867; 78OPP225; 78RCR1042; 78UK1933; 79UK793; 80H1033; 80H2015; 80MI1; 81T3423; 82MI1; 83AHC305; 85T237).

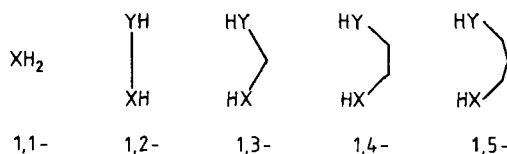
Nucleophiles used in addition and substitution reactions with pyridines, pyrimidines, pyrazines, pyridazines, triazines, tetrazines, and their benzo analogues commonly contain one reactive center, such as ammonia, amide ions (73MI1; 78ACR462; 78H33; 78UK1923; 82MI1; 83AHC305; 85T237), hydroxide ions (80H2015; 81T3423), cyanide (80H1033), hydride, methoxide ions, amines, alcohols, thiols, carbanions, and others (64AHC285; 65AHC145; 68MI1; 73KGS723; 73KGS1155; 73MI1; 73UK1415; 74KGS3; 76RCR454; 76UK908; 78ACR462; 78H33; 78KGS867; 78OPP225; 78RCR1042; 78UK1933; 79UK793; 80H1033; 80H2015; 80MI1; 81T3423; 82MI1; 83AHC305; 85T237). Also many ring transformations of pyridines, pyrimidines, triazines, and other aza-aromatics are initiated by nucleophilic attack of these reagents (73MI1; 78H33; 78KGS867; 81T3423; 85T237). Important aspects of these reactions, such as the formation of σ -adducts, the aza-activation, the leaving group mobilities, are well established and our understanding of their mechanisms is considerably progressed (76UK908; 78ACR462; 78OPP225; 79UK793; 82MI1; 83AHC305; 85T237).

Reactions of azines with bifunctional nucleophilic reagents have attracted interest only since about 1977; many reports on cyclizations and ring transformations of azines by action of dinucleophiles have appeared [see (77H391; 78H33; 78KGS867; 84H289; 84UK1648; 85KGS1011; 85T237), and references cited therein]. Novel cyclizations and ring transformation reactions have opened up new possibilities for the facile syntheses of many useful heterocycles. In particular, a number of simple and very attractive one-step syntheses of new triazaphenothiazine central nervous system depressants (77MI2) and anticancer substances, such as 5-fluorouracil (83JHC457), isocytidine (77JHC537; 78JOC1193), and other modified pyrimidine C-nucleosides (84H289), have been reported.

This article deals with reactions of azines in which bifunctional nucleophilic reagents attack two atoms of the same aza-aromatic ring to yield cyclization products. Depending on the stability of these cyclo-adducts, further rearrangement can take place, leading to products in which the ring is different from that of the starting material: a ring transformation has taken place.

II. Bifunctional Nucleophiles

Bifunctional nucleophiles can be classified, according to the nature of their nucleophilic centers, as C,C-, C,N-, C,O-, N,S-, N,N-dinucleophiles or, when taking into account their mutual positions in the molecules, 1,2-, 1,3-, 1,4-dinucleophiles, etc. (Scheme 1).

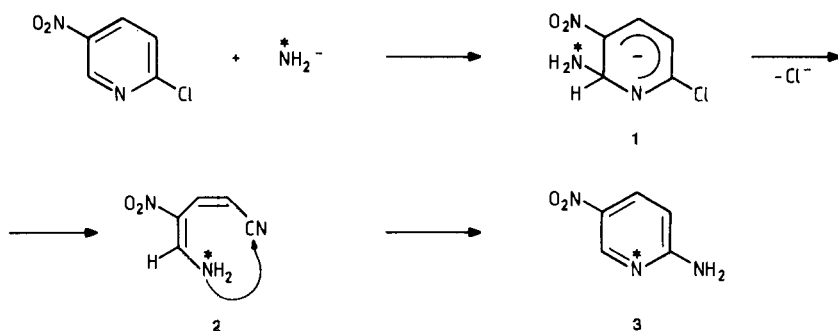


SCHEME 1

Very often one or both nucleophilic centers in such reagents are activated by deprotonating the acidic CH, OH, NH, or SH groups on treatment with bases. There are also many examples in which the same carbon or heteroatom bearing two hydrogen atoms ($-\text{CH}_2-$ or $-\text{XH}_2$) is deprotonated twice in the course of the reaction, each time participating in a nucleophilic attack on the azine ring. We regard such reagents as 1,1-dinucleophiles. In Sections IIA–E, some examples of reactions between azines and these various dinucleophiles, showing their basic reaction features, are presented.

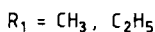
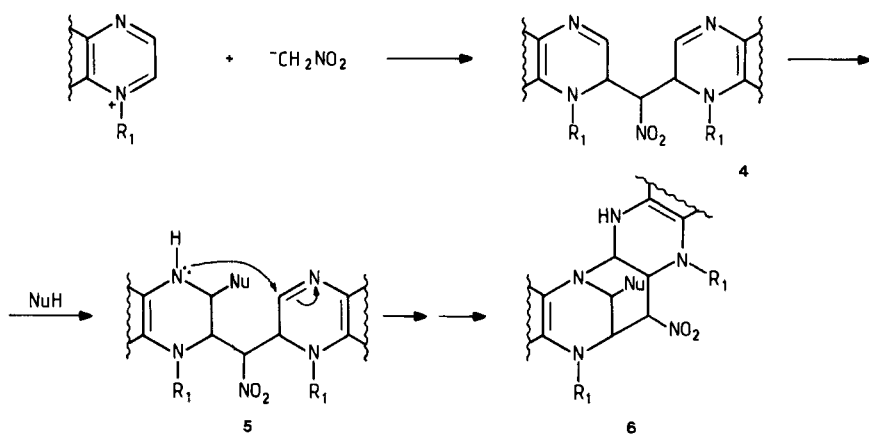
A. 1,1-DINUCLEOPHILES

Interesting examples of reactions in which a 1,1-bifunctional nucleophilic reagent is involved are the nucleophilic substitution reactions by action of ammonia or potassium amide, which proceed via the ANRORC (addition of the nucleophile, ring opening, and ring closure) mechanism (78ACR462; 82MI1; 85T237). For instance, the reaction of 2-chloro-5-nitropyridine with potassium [^{15}N] amide results in 2-amino-5-nitropyridine in which 75% of the molecules contain the ^{15}N -label on the ring nitrogen (Scheme 2) (85JOC484). The reaction involves the initial addition of the amide ion at C-6, yielding the anionic σ -adduct **1**, followed by ring opening into the open-chain intermediate **2**. The latter undergoes an intramolecular cyclization into the pyridine derivative **3**, involving the second participation of the nitrogen of the [^{15}N] amino group. Thus, in the course of the reaction, the amide ion becomes attached both to C-2 and to C-6 of the starting pyridine ring. This fact shows that the nucleophilic amide ion can actually be considered a bifunctional nucleophile.



SCHEME 2

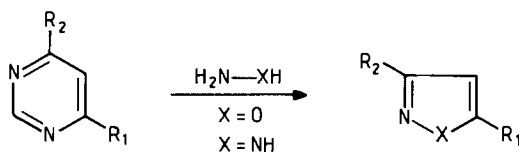
Numerous examples of this bifunctional behavior of the amide ion have been reported and extensively reviewed (85T237). Also carbanions of nitroalkanes when reacted with pyrazinium or quinoxalinium salts into the azapolycyclic compound **6** (Scheme 3) act as a 1,1-bifunctional nucleophilic reagent. The reaction can be considered to take place by an initial nucleophilic attack of the carbanion at C-2 of the pyrazinium ring, a subsequent deprotonation of the nitroalkyl side chain, followed by renewed addition at C-2 of a second pyrazinium ion giving adduct **4**. In the dihydropyrazine ring of **4**, a nucleophilic reagent can add leading to **5**, in which the nitrogen with its lone pair undergoes an internal cyclization yielding **6** (Scheme 3) (85TL515; 86KGS389).



SCHEME 3

B. 1,2-DINUCLEOPHILES

Hydrazine and hydroxylamine are the most widely used 1,2-dinucleophiles. A great number of ring transformation reactions by action of these reagents have been discovered and are presented in a monograph (73MI1) and review articles (72UK1788; 78H33). One of the reactions of this type is shown in Scheme 4 (72UK1788).

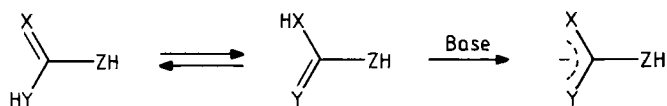


SCHEME 4

C. 1,3-DINUCLEOPHILES

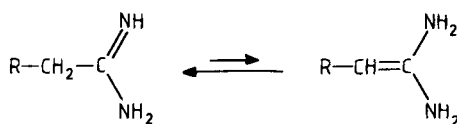
1,3-Bifunctional nucleophilic reagents, such as ketones, enamines, β -diketones and their derivatives, amidines, thioureas, thioamides, dithiocarbamates, and others, are very often employed in cyclizations with azine derivatives, resulting in the formation of annelated five-membered cycles (84UK1648; 85KGS1011). The structure of all these 1,3-dinucleophiles feature a double bond conjugated with an anionic center or with a heteroatom bearing the lone pair of electrons (Scheme 5).

The characteristic feature of these three-centered unsaturated systems is their ability to undergo prototropic conversions. Ketone–enol, thione–thiol, enamine–imine, and other types of triad tautomerism are well-known; some other examples of tautomeric conversions, in particular the existence of enediamines as tautomer of acetamidines, have been confirmed experimentally (Scheme 6) (81SC655; 83JOC2667).



X, Y, Z : CHR, NR, O and S

SCHEME 5



SCHEME 6

A great variety of reactions between azines and 1,3-dinucleophiles proceed only in the presence of a base. Under basic conditions, 1,3-tautomeric systems form ambident anions (Scheme 5). They can give rise to several types of σ -adducts, which differ by the site of the azine ring on which the addition takes place, as well as the nature of the atom X, Y, or Z which attached to the sp^3 -center in the adduct. The tautomerism and ambident properties of 1,3-dinucleophilic reagents should be taken into account when considering their behavior in cyclizations with aza-aromatic substrates (84UK1648). It is also worth mentioning that in dinucleophilic reagents the second nucleophilic center sometimes develops only during the cyclization reaction. An example is the enamine of a ketone, which reacts with *N*-alkylquinoxalinium salts to form the cyclization products **9** and **10** (Scheme 7) (79DOK351; 80ZOR1064). Although in the enamine the second carbanionic center is absent, in compound **7**, being the intermediate in the reaction, the carbon in the ortho position of the iminium group is deprotonated, generating the second carbon nucleophilic center, which can add to the ortho position of the dihydropyrazine ring, yielding **9**. All attempts to register σ -adducts like **8** by means of ^1H -NMR spectroscopy at low temperatures failed.

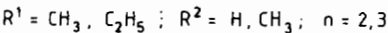
D. 1,4-DINUCLEOPHILES

A great variety of 1,4-dinucleophiles have also been employed in cyclizations with azines (85KGS1011). Among them are 1,2-diamines, 1,2-aminothiols, 1,2-amino alcohols, and their structural analogues, such as thiosemicarbazides, amidoximes, dithiocarbazates, etc. (Scheme 8).

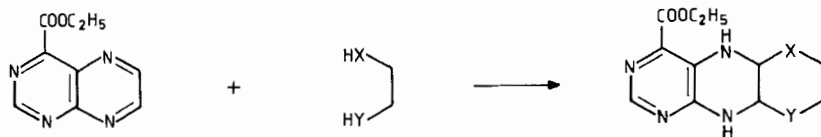
The reaction of pteridines with 1,2-diamines, diols, and dithiols can serve as an example (Scheme 9) (71JCS(C)371).

E. OTHER DINUCLEOPHILES

There are several examples known of participation of azines in cyclizations with 1,5- and 1,6-dinucleophiles (77T981; 84H743, 84H1017). Reaction of the thia analogue of isoalloxazine **11** with bifunctional nucleophiles has been

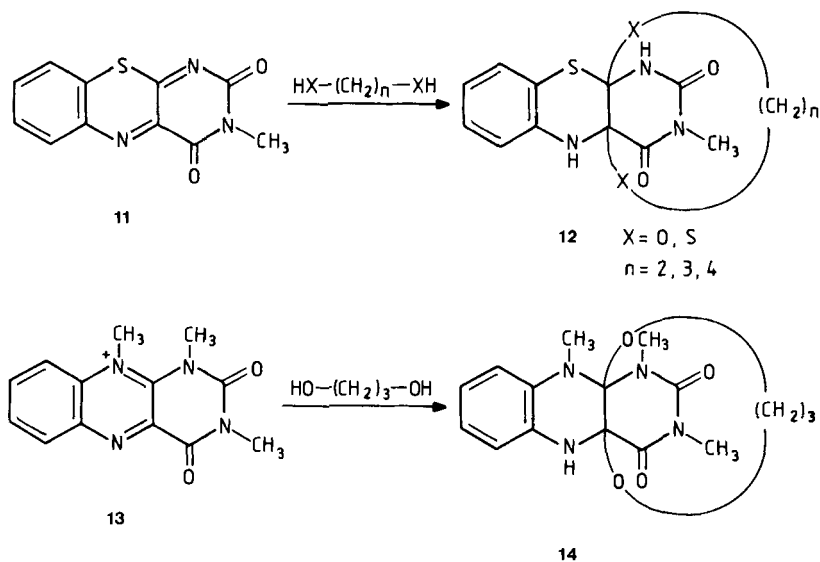


$\text{H}_2\text{N}-\text{CH}_2-\text{X}$ $\text{HS}-\text{CH}_2-\text{CH}_2-\text{SH}$ $\text{H}_2\text{N}-\text{N}(\text{R})-\text{C}(\text{X})=\text{S}$ $\text{H}_2\text{N}-\text{C}(\text{R})=\text{N}-\text{OH}$ $\text{H}_2\text{N}-\text{N}=\text{C}(\text{CH}_3)-\text{COR}$
 $\text{X} = \text{NH}_2, \text{OH}, \text{SH}$ $\text{X} = \text{NH}_2, \text{SH}$



$X, Y = 0, N, S$

SCHEME 9



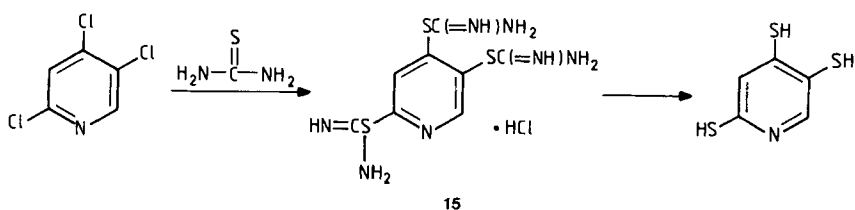
SCHEME 10

found, as could be expected, to be dependent on the chain length in the binucleophilic reagent (Scheme 10) (84H743, 84H1017). The cyclization products **12** are formed with dithiols ($X = S$, $n = 2, 3$) and diols ($X = O$, $n = 2-4$); however, with 1,1-diols and 1,1-dithiols (1,3-dinucleophiles), no reaction takes place. Just the presence of one methylene group between both nucleophilic groups makes the distance between these groups too short to achieve formation of the cycloadducts **12** (Scheme 10) (84H743, 84H1017).

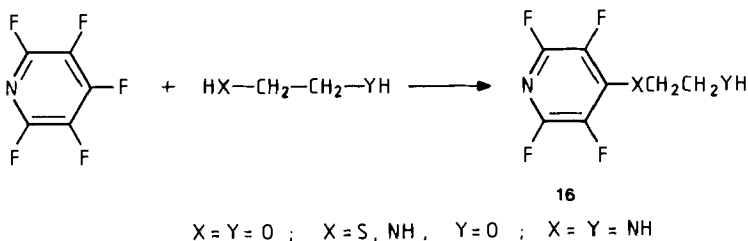
The same feature is observed in the diaddition reaction of diols to the alloxazinium cation **13**, affording compound **14** (Scheme 10) (77T981).

III. Reactions of Azines with Bifunctional Nucleophiles

Reactions of azines with bifunctional nucleophiles usually lead to cyclization or ring-transformation products. There are, however, numerous examples of reactions in which nucleophilic reagents having potentially two or even more reactive centers act only with one of these centers to give rise to the formation of the usual ipso products. For instance, 2,4,5-trichloropyridine, when reacting with thiourea (a potential 1,3-dinucleophile), gives only the corresponding 2,4,5-trimercaptopyridine via intermediate **15**; the cyclization reaction into a thiazolo-annulated pyridine has not been observed (Scheme 11) (78AJC389).



SCHEME 11

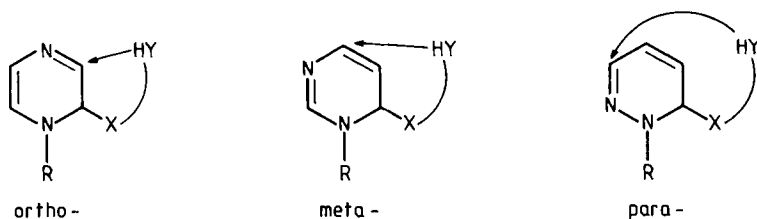


SCHEME 12

Similarly, treatment of pentafluoropyridine with various dinucleophiles yields the substitution products **16** (Scheme 12). No cyclization products have been observed (75RC1039).

These examples seem to indicate that the interaction of azines with bifunctional nucleophiles can result in the formation of cyclization products only if we deal with an azine in which the reactivity of the leaving groups is enhanced by aza-activation or by the presence of electron acceptors. It has been found indeed that diazines, triazines, etc., are more inclined to cyclization than are pyridines.

Depending on the mutual positions of aza groups or substituents in the substrate, the secondary nucleophilic attack can be directed into ortho, meta, or para positions, relative to the ring atom already attached to the bifunctional reagent (Scheme 13). In ortho-cyclizations, two atoms of the azine ring become the ring junction atoms of condensed systems, while in meta- and para-cyclizations one or two atoms, respectively, of the azine ring become bridging atoms. Which type of cyclization occurs depends on the number and position of the nitrogen atoms in the azine and the nature of the dinucleophile employed. When considering the series of diazines, one can expect that, in reactions with bifunctional nucleophilic reagents, pyrazines will form condensed azine systems, while pyrimidines and pyridazines are expected to form meta- and para-bridged cyclization products, respectively (Scheme 13).



SCHEME 13

A. ORTHO-CYCLIZATIONS BASED ON DISUBSTITUTION REACTIONS

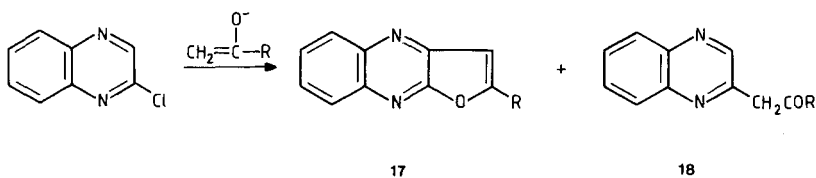
Reactions of pteridines, quinoxalinium, and alloxazinium salts with bifunctional nucleophilic reagents as exhibited above in Schemes 7, 9, and 10 show examples of ortho-cyclizations. They proceed mainly in the series of 1,4-diazines, although examples of the participation of other azine derivatives in ortho-cyclizations with dinucleophiles are also known (85KGS1011).

Ortho-cyclizations mentioned in Schemes 7, 9, and 10 proceed by diaddition of the bifunctional nucleophiles to the azine ring. It is, however, also possible that ortho-cyclization occurs by substitution of two nucleofugic groups attached to two neighboring carbons of the azine ring. Especially the last mentioned method is successfully applied. Reactions of *o*-dihalogeno- or *o*-nitrohalogenoazine derivatives with dinucleophiles usually result in the formation of condensed heterocyclic compounds in which the azine ring is fused with a variety of five- and six-membered heterocycles (85KGS1011; 77H391, 77M11). 2,3-Dichloroquinoxaline is a favored compound for cyclizations with bifunctional nucleophilic reagents because of the high mobilities of both chloro atoms and its symmetrical structure avoiding the formation of isomeric cyclization products. In the following sections a number of examples will illustrate this principle.

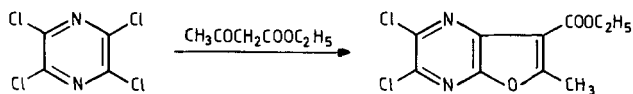
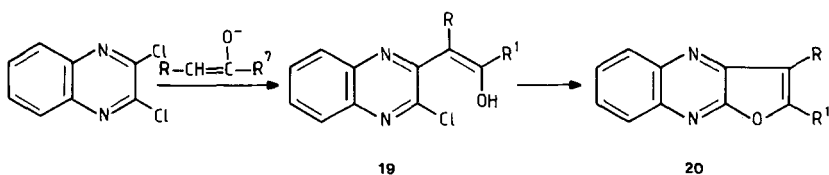
1. *Annellation of Five-Membered Heterocycles to Azines*

a. *Furoazines*. 2-Chloroquinoxaline reacts with ketone enolates mainly to form furo[2,3-*b*]quinoxalines **17** together with some quinoxaliny ketone **18** as by-product (Scheme 14) (75YZ774; 82JOC1036).

Cyclization of 2,3-dichloroquinoxaline with ketone enolates gives rise to similar products **20**; the reaction, however, proceeds under milder conditions and gives higher yields in comparison to monohalogeno-1,4-diazines (Scheme 15) (72YZ736).



SCHEME 14

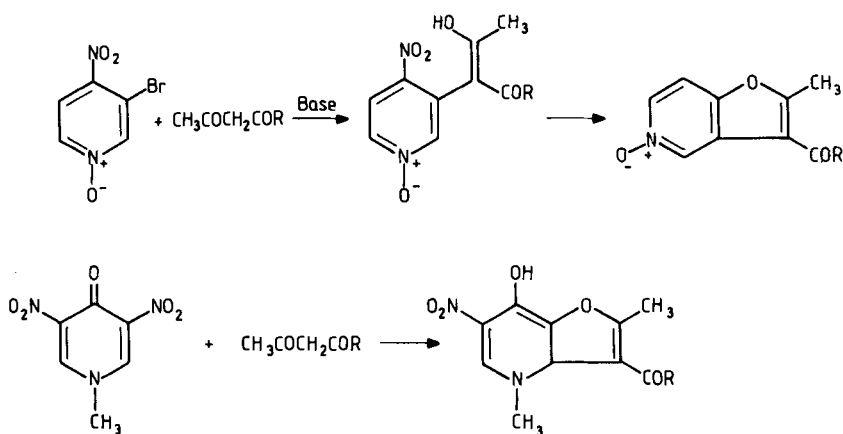


SCHEME 15

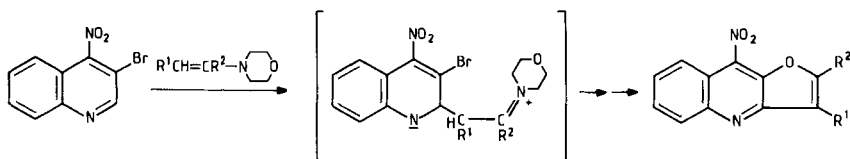
The furo[2,3-*b*]quinoxalines **20** are formed only in cases where the keto group in the intermediate quinoxaliny ketone **19** is enolizable. If enolization is not possible, the reaction is completed by the formation of product **19** (Scheme 15) (72YZ736). Therefore, it is not surprising that β -dicarbonyl compounds, which are considerably enolized, undergo a very smooth cyclization with tetrachloropyrazine; with ethyl acetoacetate, furo[2,3-*b*]pyrazine is obtained in good yield (Scheme 15) (83JHC365).

The furan ring is also formed in reactions of β -dicarbonyl compounds with a number of pyridines which are activated by the presence of the strong electron-accepting nitro group (Scheme 16) (73BCJ3144; 76H453; 80BCJ2891).

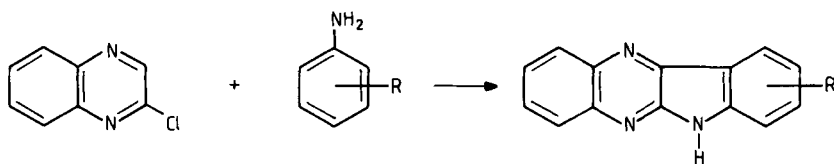
Interestingly, furan ring annelation is also found in the reaction of 3-bromo-4-nitroquinoline with enamines. Due to hydrolysis of the iminium intermediate, the keto group is formed, which after enolization is able to act in the intramolecular cyclization with expulsion of bromide ion (Scheme 17) (76H453). The nucleophilic substitution of hydrogen at C-2 is preferred to that of the nitro group at C-4.



SCHEME 16



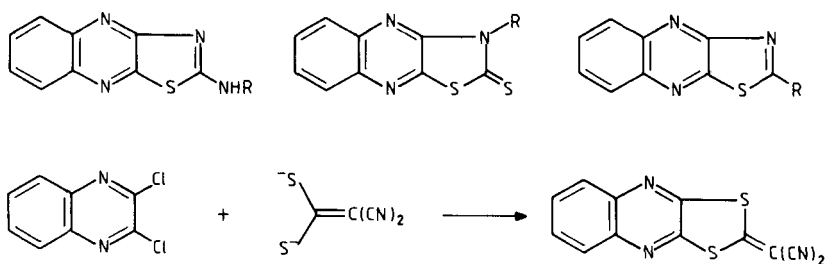
SCHEME 17



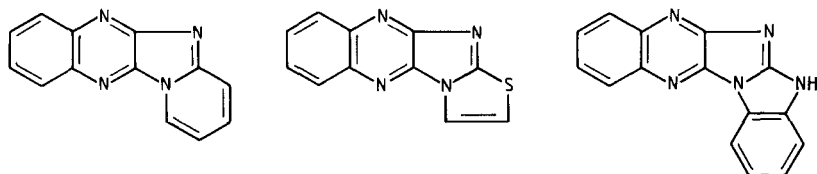
SCHEME 18

b. Pyrrolo-, Thiazolo-, and 1,3-Dithiolozines. Using arylamines as 1,3-C,N-dinucleophiles in the reaction with 2-chloroquinoxaline, indoloquinoxalines can be obtained (Scheme 18) (78T981). Similarly, pyrrolopyridines and pyrrolopyridazines have been obtained on reaction with pyridine and pyridazine derivatives (85KGS1011).

Various thiazolo[4,5-*b*]quinoxalines, formed by the cyclization of 2,3-dichloroquinoxaline with thioureas (76JIC1170; 77ZC15; 78IJC(B)683;



SCHEME 19



SCHEME 20

80JIC946), dithiocarbamates (76JIC1170; 80JIC946), thioamides (80JIC946; 81G409), or other 1,3-N,S-dinucleophiles (74IJC966; 79IJC(B)364; 82JHC77), have been reported (Scheme 19).

Sodium or ammonium salts of 1,1-dithiols have been used as 1,3-S,S-dinucleophiles for the annelation to the thiolane ring (Scheme 19) to quinoxaline (78USP4075209).

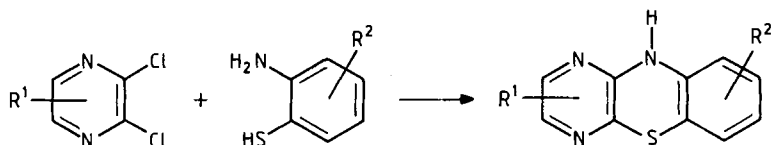
c. Azines Condensed with Other Five-Membered Heterocycles.

2-Amino derivatives of nitrogen-containing heterocycles have been reported to react with 2,3-dichloroquinoxaline as cyclic amidines to produce condensed imidazoquinoxalines in good yields (Scheme 20) (81G409).

In conclusion, a great number of azine derivatives condensed with five-membered rings can be obtained by means of disubstitution reactions with a variety of 1,3-dinucleophiles, provided that the positions in which the addition or substitution takes place are activated.

2. Annelation of Six-Membered Heterocycles to Azines

The reactions of *o*-dihalogenoazines and *o*-halogenonitroazines with various 1,4-dinucleophiles appear to be a very fruitful, most frequently applied method for achieving annelations of six-membered heterocycles to the azine ring.



SCHEME 21

a. *Phenothiazines*. Ortho-cyclizations of azines with bifunctional reagents such as *o*-aminothiophenols have attracted the attention of many chemists as simple synthetic routes to aza-analogues of phenothiazines, a class of compounds which exhibit high tranquilizing activities (57YZ485; 58JA1651; 59JOC1156; 64USP3106581; 73JOC4386; 74IJC287; 74USP3808208; 75JHC813; 77MI1; 78JIC817; 78PS79; 80JHC149; 80JHC1587; 81G413; 81JHC405; 81JHC799; 81JHC1589; 82JOC592; 83JHC1047; 83JMC564; 85KGS131; 85KGS1011). Because of reasons mentioned above, 2,3-dichloro-1,4-diazines in particular have been frequently used as substrates in the annelation reactions (Scheme 21) (74IJC287; 74USP3808208; 77MI1; 78JIC817; 78PS79; 80JHC149; 80JHC1587; 81G413; 81JHC405; 81JHC1589; 82JOC592; 83JMC564).

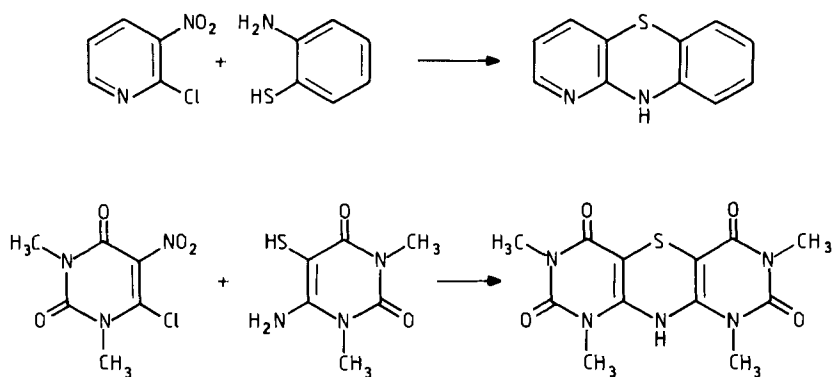
Similar cyclizations of aminophenols and their aza-analogues with 2-chloro-3-nitropyridines (57YZ485; 58JA1651; 59JOC1156; 64USP3106581), 4,5-dichloropyridazin-3(2*H*)-one (83JHC199), pyrimidines (73JOC4386; 75JHC813; 85KGS131), and other azines derivatives have also been reported (Scheme 22).

Several triazaphenothiazines have been obtained in reactions of dihalogenopyrimidines with aminomercaptopyridines, as illustrated in Scheme 23 (73JOC4386). The first stage in these cyclizations is the substitution of halogen at C-4(6) of the pyrimidine ring by the amino group, regardless of whether its position in the pyridine ring is at C-2 or C-3 (73JOC4386).

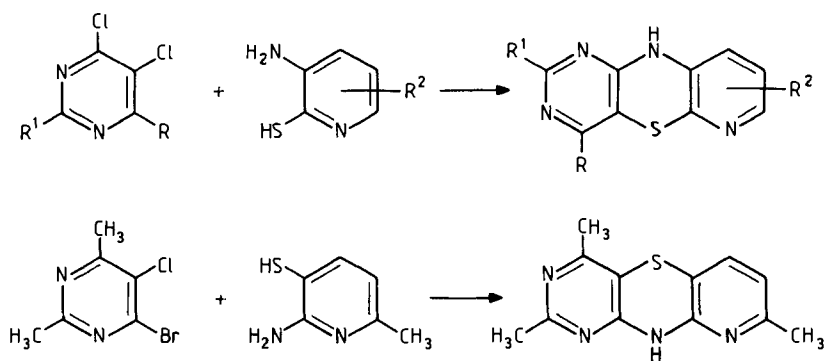
b. *Dithiinoazines*. The annelation reaction leading to 1,4-dithiinoazines was studied extensively since several of these compounds were found to possess high antibacterial and/or antifungal activities (75USP3853901).

Dithiinopyrazines have been obtained by the cyclizations of 2,3-dichloropyrazine with 1,2-dimercapto compounds (Scheme 24) (75USP3853901) and double 1,4-dithiine annelation has been observed in the reaction of tetrachloropyrazine with 1,2-dimercapto-1,2-dicyanoethylene (Scheme 24) (75USP3843644; 75USP3853901).

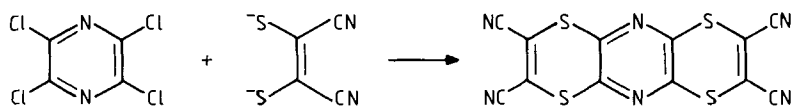
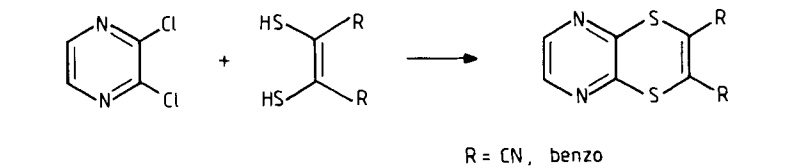
Polyhalogenopyridazines were also found to react smoothly with 1,4-S,S-dinucleophiles to yield dithiinopyridazines (Scheme 25) (75USP3849415).



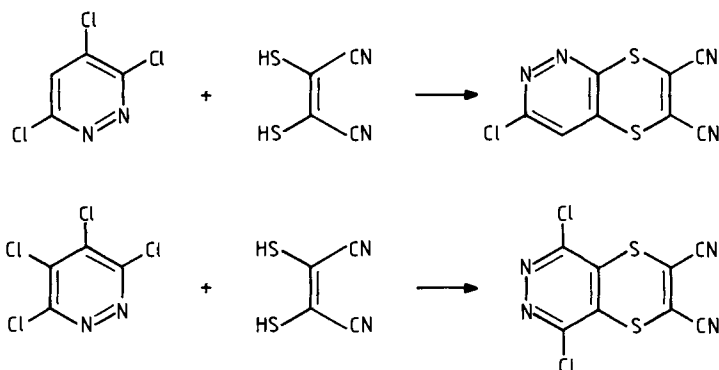
SCHEME 22



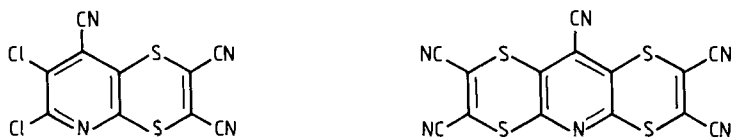
SCHEME 23



SCHEME 24



SCHEME 25



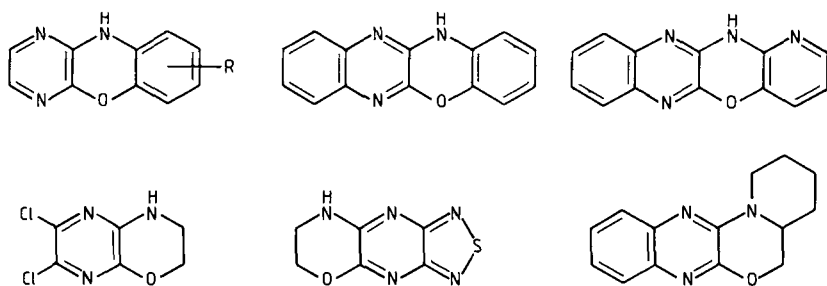
SCHEME 26

4-Cyano-2,3,5,6-tetrachloropyridine undergoes a smooth cyclization with one as well as two molecules of 1,2-dimercaptoethylene to yield bicyclic or tricyclic pyridines, respectively (Scheme 26) (74USP3829425).

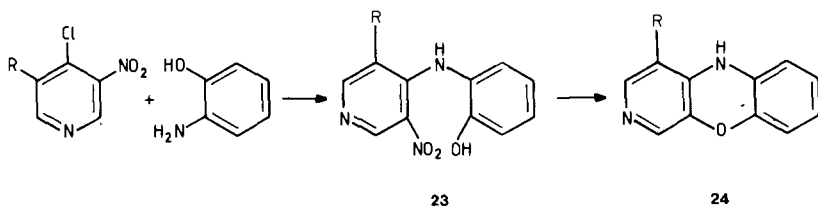
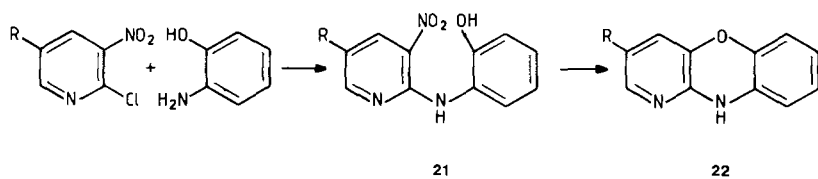
c. Oxazinoazines. For the preparation of a pyrazine ring system that is condensed with the 1,4-oxazine ring, various 1-hydroxy-2-amino compounds have been employed in the reaction with 2,3-dichloro-1,4-diazines (74USP3808208; 77USP4029657; 78USP4080499; 79JHC1025; 79JHC1345; 81JHC1445). Some examples of compounds obtained are shown in Scheme 27.

In reactions of halogenonitropyridines with *o*-aminophenol leading to the azaphenoxazines **22** and **24**, respectively, the intermediary monosubstitution products **21** and **23** could be isolated, showing that the first step in the cyclization is the aminodechlorination reaction (Scheme 28) (45JCS313; 78CPB1375). The second stage of the cyclization reaction involves an intramolecular phenoxy-denitration. The intramolecular nucleophilic substitution of the nitro group in azine derivatives has been discussed in a review (82KGS867).

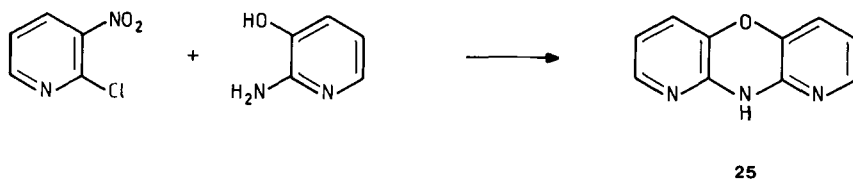
The cyclization of 2-chloro-3-nitropyridines with 2-amino-3-hydroxypyridine proceeds in a similar way to afford the diazaphenoxazine **25** (Scheme 29) (74CC878; 76JHC107; 77H391; 77JPS1349).



SCHEME 27



SCHEME 28



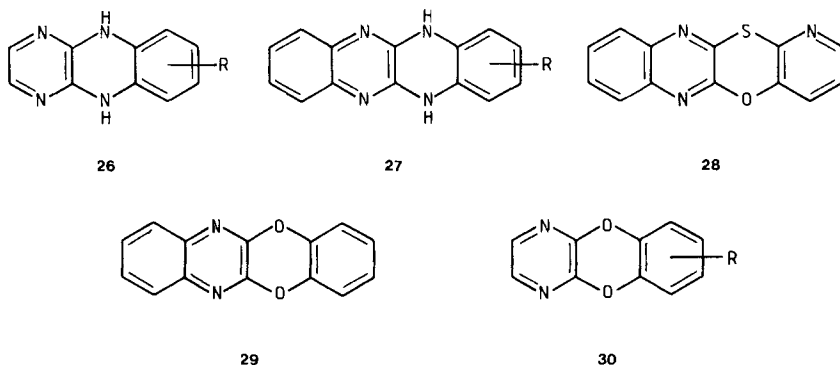
SCHEME 29

Cyclizations of azines with N,O- and N,S-dinucleophiles proceed via a two-step mechanism also involving in the first stage an amino-dehalogenation, leading to the formation of N-substituted products, followed by an intramolecular cyclization into the corresponding heterocyclic systems (77JPS1349; 77USP4029657; 79JHC1025; 81JHC1169; 81JHC1445).

d. *Azines Condensed with Other Six-Membered Heterocycles.* There are only a few papers dealing with the cyclizations of 1,4-diazines with 1,4-N,N-, 1,4-O,S-, and 1,4-O,O-dinucleophiles; condensed pyrazines, such as **26** and **27** (77JPS1349; 81G413), oxathiines **28** (81JHC1169; 83JHC1063), and dioxines, such as **29** and **30** (Scheme 30) (75JCS(P1)534; 81G413) are formed.

Similar reactions could also be performed on *o*-dichloro-substituted pyridazines (Scheme 31) (75JCS(P1)534; 81JHC1165; 82JHC1447).

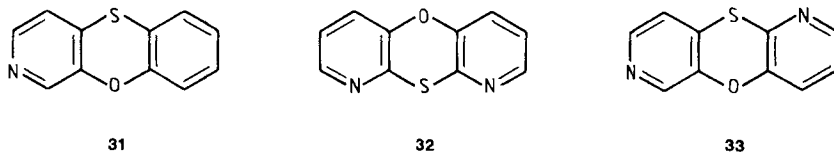
There are also some reports on the formation of the oxathiine derivatives **31–33**, resulting from cyclizations of 2-chloro-3-nitro- and 4-chloro-3-nitropyridines with 1,4-O,S-bifunctional nucleophiles (Scheme 32) (81JHC479; 80JHC589; 79TL5035; 80JHC1153).



SCHEME 30



SCHEME 31



SCHEME 32

B. ORTHO-CYCLIZATIONS BASED ON DIADDITION REACTIONS

As shown above, a number of ortho-cyclizations of azines with bifunctional reagents have been performed by substitution of two adjacent nucleofugic groups and allow the syntheses of a great variety of condensed azine derivatives. The obvious limitation of this method is that it can only be applied to those aza-aromatics which contain two good leaving groups oriented in ortho positions to each other.

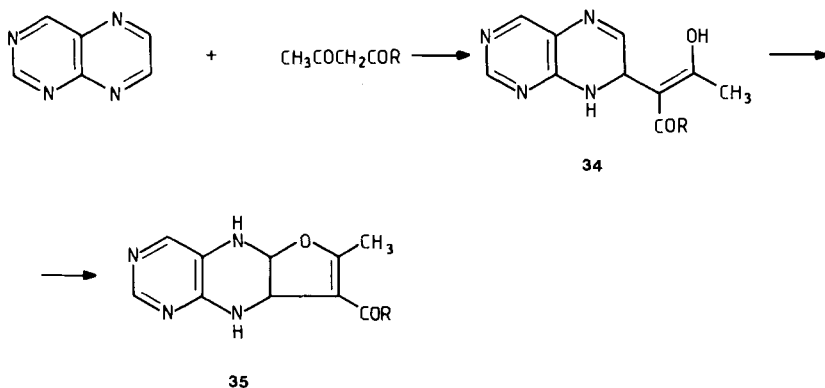
Another approach to the synthesis of condensed azine derivatives (84UK1648; 85KGS1011) is based on the ability of a number of azine derivatives to undergo diaddition reactions with nucleophiles. When bifunctional nucleophilic reagents are used, these additions result in the formation of cyclization products. In all these reactions the tetrahydro analogues of the fully unsaturated heterocyclic systems are obtained.

The reaction of pteridine with β -dicarbonyl compounds leading to the formation of the tetrahydrofuro[2,3-*g*]pteridines **35** seems to be the first example of such ortho-cyclizations (Scheme 33) (73JCS(P1)1615).

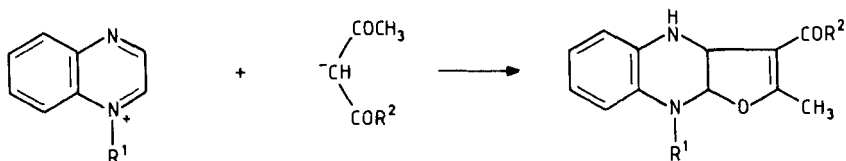
The cyclization was suggested to proceed via a two-step mechanism involving as initial step Michael addition at C-7 yielding **34**, followed by the intramolecular nucleophilic attack of the enolate oxygen at C-6 (73JCS(P1)1615).

A similar cyclization has been found to take place in the reaction of *N*-alkylquinoxalinium salts with β -dicarbonyl compounds, affording tetrahydrofuro[2,3-*b*]quinoxalines (Scheme 34) (81H195).

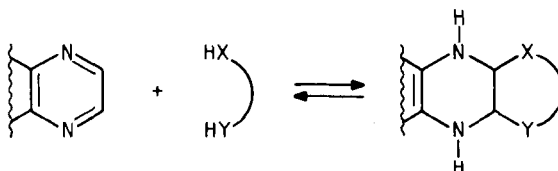
The examples of ortho-cyclizations presented in Schemes 33 and 34 and those given in Schemes 7, 9, and 10 (Sections IIC, IID, and IIE) show that 1,4-diazines, as well as 1,4-diazinium cations, are appropriate substrates to



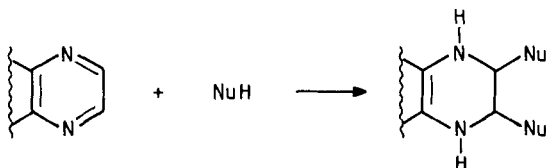
SCHEME 33



SCHEME 34



SCHEME 35



SCHEME 36

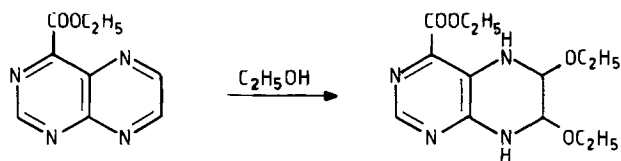
undergo addition by bifunctional nucleophilic reagents yielding cyclization products (Scheme 35).

The ability of the pyrazine ring to add monofunctional nucleophilic reagents across both C=N bonds to give diadducts (Scheme 36) has been well established. Since diaddition reactions are important for a better understanding of the nature of cyclizations, we report briefly on the results of studies on the diaddition of mononucleophilic species to 1,4-diazines.

1. Diaddition Reactions with Mononucleophilic Species

There are numerous examples of the formation of diadducts in reactions of 1,4-diazines with water, alcohols, ammonia, amines, and other simple nucleophiles.

Literature data show that diaddition reactions in the series of 1,4-diazines are favored in the case when the stability of diadducts formed is enhanced by



SCHEME 37

benzo-annellation and/or introduction of electron-withdrawing substituents (84UK1648). Among the uncharged 1,4-diazines, pteridine derivatives seem to be the most reactive since only these compounds are able to add two molecules of ammonia, amines (71JCS(C)2357; 74JCS(P1)357; 75RTC45; 760MR607), or ethanol (67JCS(C)1543) without any base catalysis (Scheme 37). However, it has become known that introduction of two trifluoromethyl groups onto the pyrazine ring of pyrido[2,3-*b*]pyrazine and pteridine stabilizes the formation of neutral covalent dihydrates in which the pyrazine ring is selectively hydrated (86JCS(P1)1043).

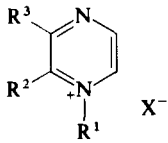
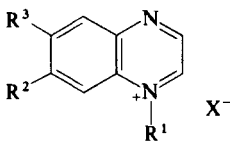
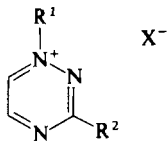
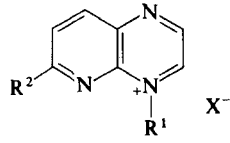
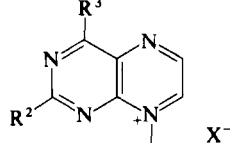
Protonated 1,4-diazines are certainly more reactive toward nucleophilic reagents than the corresponding uncharged substrates. The formation of diadducts in reactions of protonated pyridopyrazines (63JCS5737; 66JCS(C)999; 75AG(E)354; 79JHC301), pyrazino[2,3-*b*]pyrazine (66JCS(B)1105), and pteridines (66JCS(B)1105; 67JCS(C)1543; 71JCS(C)375; 71JCS(C)2278; 75AG(E)354; 75JA5540; 760MR607) with water has been observed by 1H - and ^{13}C -NMR spectroscopy (75AG(E)354; 76AHC117). Nevertheless, protonated 1,4-diazines are of limited use in reactions with nucleophiles, because of the possibility of proton transfer from the protonated substrate to the nucleophile employed.

N-alkyldiazinium salts are also highly reactive toward nucleophiles and, what is important, these reactions can be carried out in the presence of a base. This allows a great variety of nucleophiles, such as amines (73JOC1949; 85KGS669), the hydroxide ion (80H2015), and methoxide ions (72CJC919; 85KGS669; 86KGS1380) to react with *N*-alkyldiazinium cations.

In the series of *N*-alkyl-1,4-diazinium salts **36–40**, great attention was paid to the abilities of these compounds to form either mono- or diadducts. The stabilities of the σ -adducts formed were varied to a great extent either by the introduction of an aza group and/or substituents into the pyrazine ring or annellation of the latter with a benzene, pyridine, or pyrimidine ring (86KGS1380).

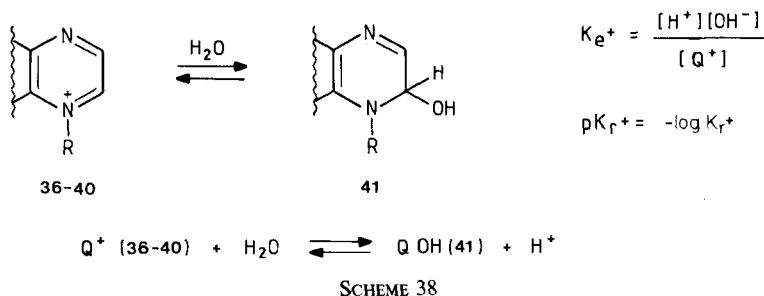
The electrophilicities of the cations were determined by measuring their reduction potentials. They were found to cover a wide range, as follows from the data given in Table I.

TABLE I
 POLAROGRAPHIC REDUCTION POTENTIALS OF N-ALKYL-1,4-DIAZINIUM SALTS^{a,b}

Structure	Compound	R ¹	R ²	R ³	E _{1/2} (V)	pK _{R+} ^c
	36a	CH ₃	H	H	-0.75	—
	36b	C ₂ H ₅	H	H	-0.67	—
	36c	CH ₃	H	CONH ₂	-0.50	8.04
	36d	CH ₃	H	COOCH ₃	—	6.37
	36e	C ₂ H ₅	COOCH ₃	COOCH ₃	-0.20	3.22
	37a	CH ₃	H	H	-0.34	8.62 ^e
	37b	CH ₃	H	H	-0.37	8.62
	37c	C ₂ H ₅	H	H	-0.36	9.26
	37d	C ₂ H ₅	H	H	-0.37	9.26
	37e	CH ₃		Benzo	-0.16	5.73
	37f	C ₂ H ₅		Benzo	-0.18	6.32
	38a	CH ₃	NC ₄ H ₈ O ^e		-0.45	—
	38b	C ₂ H ₅	NC ₄ H ₈ O ^e		-0.45	—
	39a	CH ₃	N(CH ₃) ₂		-0.56	12.50
	39b	CH ₃	NC ₅ H ₁₀ ^f		—	12.50
	39c	CH ₃	NC ₄ H ₈ O ^e		-0.51	—
	40a	C ₂ H ₅	H	NC ₄ H ₈ O ^e	-0.26	5.00
	40b	C ₂ H ₅	SCH ₃	NC ₄ H ₈ O ^e	-0.30	7.01
	40c	CH ₃	N(CH ₃) ₂	CH ₃	-0.32	7.24
	40d	C ₂ H ₅	NC ₄ H ₈ O ^e	CH ₃	-0.29	6.74
	40e	C ₂ H ₅	NC ₅ H ₁₀ ^f	CH ₃	-0.35	7.63

^a In dimethylformamide.^b X = J for 36a,c,d, 37a,c,e, 38a, 39a-c; BF₄ for 36b,e, 37d,f, 38b, 40a,b,d,e; ClO₄ for 37b; and SO₃F for 40c.^c Reference (86KGS1380).^d Reference (72CJC919).^e Morpholino.^f Piperidino.

Another characteristic value which describes in quantitative terms the tendency of 1,4-diazinium cations to interact with the hydroxide ion in a monoaddition reaction is the pK_{R+} value. These values give some indication about the stabilities of the hydroxy adducts (Scheme 38) (86KGS1380).



The variation of pK_{r^+} values in the series of the *N*-alkyl-1,4-diazinium cations **36–40** shows that the stabilities of the hydroxy adducts **41** increase by (1) introduction of electron-withdrawing substituents onto the pyrazine ring, (2) hetero-aromatic annelation, and (3) aza-activation (Table I). Thus, the 2,3-dimethoxycarbonyl-substituted pyrazinium ion **36e**, benzo[*g*]quinoxalinium **37e,f** and 8-alkylpteridinium salts **40a–e** have profound tendency to form stable hydroxy adducts **41**. In contrast, no indications for adduct formation have been found in the reaction of unsubstituted *N*-alkylpyrazinium salts **36a,b** and 1,2,4-triazinium salts **38a,b** with the hydroxide ion, and consequently pK_{r^+} values for these cations could not be obtained.

Although the reactivities of the 1,4-diazinium cations mentioned in Table I differ considerably, the majority of them are able to undergo the monoaddition reaction with hydroxide ion.

The methoxy σ -adducts **42–44** have been observed by 1H and ^{13}C NMR in the reactions of pyrazinium, quinoxalinium, and pteridinium cations with the methoxide ion (Scheme 39). Measured in methanol- d_4 at 20°C, the hydrogen attached to the sp^3 -carbon atom in the methoxy adducts **42–44** has undergone an upfield chemical shift (between 5.3 and 5.5 ppm) when compared with the chemical shift of the hydrogen on the sp^2 -carbon atom C-2 in **36**, **37**, and **40** respectively; in the ^{13}C -NMR spectra, the sp^3 -carbon atom shows an upfield chemical shift between 80.3 and 84.3 ppm (Table II) (86KGS1380).

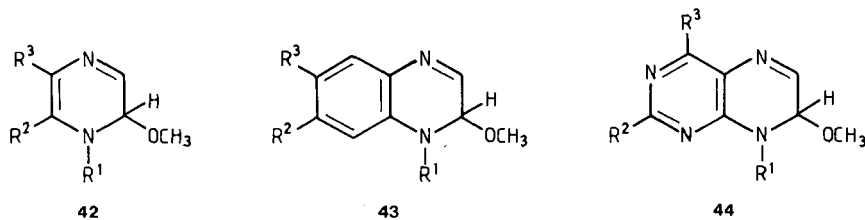


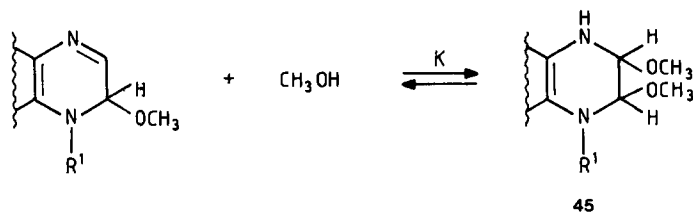
TABLE II
¹H AND ¹³C CHEMICAL SHIFTS FOR THE DIHYDROPYRAZINE
 FRAGMENT IN THE ¹H- AND ¹³C-NMR SPECTRA OF THE METHOXY
 ADDUCTS 42–44^a

Starting azinium cation	Adduct	The dihydropyrazine ring			
		$\delta(^1\text{H})$ (ppm)		$\delta(^{13}\text{C})$ (ppm)	
		H- α	H- β	C- α	C- β
36c	42a	5.38	7.03	82.3	138.1
36d	42b	5.44	7.09	82.1	139.4
36e	42c	5.42	7.18	80.3	139.5
37a	43a	5.32	7.60	83.5	149.4
37e	43b	5.32	^b	81.6 ^c	155.6 ^c
40a	44a	5.50	7.36	82.3	143.2
40b	44b	5.38	7.18	84.3	143.5
40c	44c	5.41	7.22	84.2	144.3
40d	44d	5.55	7.25	82.9	144.5
40e	44e	5.48	7.16	83.0	143.6

^a In methanol-*d*₄ at 20°C.

^b Under the multiplet of aromatic protons.

^c In CDCl₃.



SCHEME 40

In the secondary addition of methanol to the monomethoxy adducts 42–44, their reactivities vary to the greater extent. It has been established by ¹H-NMR spectroscopy that diaddition of sodium methoxide in methanol-*d*₄ occurs at 20°C with the 1,4-diazinium salts 36e, 37a,c,f, and 40d (Scheme 40) (86KGS1380). Monosubstituted pyrazinium salts 36c,d as well as the pteridinium cations 40a,b do not produce any detectable quantities of the dimethoxy adducts 45.

Equilibrium constants *K* for the formation of dimethoxy adducts 45 (Table III) show that benzo[*g*]quinoxalinium salt 37f is the most reactive in

TABLE III
EQUILIBRIUM CONSTANTS FOR THE FORMATION OF DIMETHOXY ADDUCTS **45**^{a,b}

Starting <i>N</i> -alkyl- 1,4-diazinium salt	Monomethoxy adduct	Dimethoxy adduct	<i>K</i> (liter/mol)
36e	42e	45e	1.6×10^{-2}
37a	43a	45a	2.4×10^{-2}
37c	43c	45c	2.4×10^{-2}
37f	43f	45f	1.2×10^{-1}
40d	44d	45d	1.8×10^{-3}

^a In methanol-*d*₄ at 20°C.

^b Letters **a–f** refer to the substituents given in Table I for the different 1,4-diazinium cations.

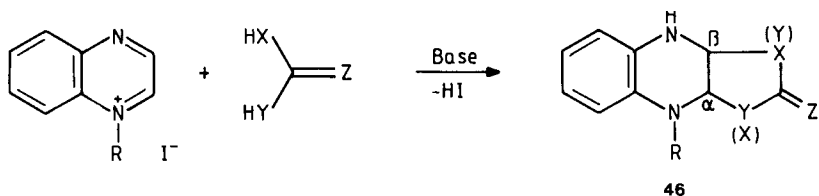
the diaddition reaction with methanol. Quinoxalinium salts **37a,c** show less tendency to form diadducts, but they are more reactive than the pteridinium cation **40d**.

The ability of methoxy adducts **42–44** to add a second molecule of methanol across the C=N bond appears to depend on the C=N carbon electrophilicity. The latter can be estimated by chemical shifts for proton and carbon-13 resonances of the HC=N fragment in the ¹H- and ¹³C-NMR spectra of dihydropyrazines **42–44**.

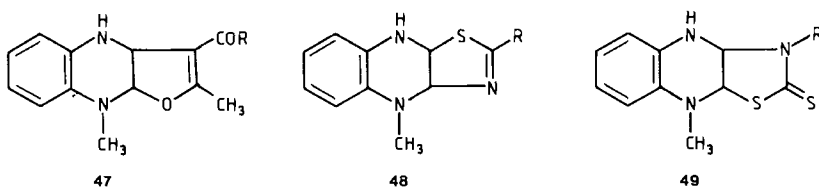
The ¹³C-chemical shifts are particularly illustrative in this respect. In the ¹³C-NMR spectra of compounds **42–44**, the C=N carbons of dihydropyrazines **42** resonate at higher fields (138–139 ppm) than those of dihydropteridines **44** (143–144 ppm), while in dihydroquinoxalines **43a,b**, the β-carbon is most deshielded (149 and 155 ppm) (Table II). More shielding suggests an increase in local electron densities on the β-carbon and, as a consequence, a decrease in electrophilicities. This leads to a decrease of diadduct formation in the following sequence: dihydroquinoxalines **43** > dihydropteridines **44** > dihydropyrazines **42**. This sequence order is in good agreement with experimental results on cyclizations of 1,4-diazinium cations with bifunctional nucleophiles.

2. Annelation of Five-Membered Rings

A large number of ortho-cyclizations with 1,3-dinucleophiles has been performed on the readily accessible quinoxalinium salts **37**, which, as we have seen, show a great tendency to undergo diaddition. A number of one-step syntheses of furoquinoxalines (81H195; 81KGS1392; 81KGS1543; 85KGS669), pyrroloquinoxalines (81DOK384; 81KGS843; 81KGS1549;



SCHEME 41

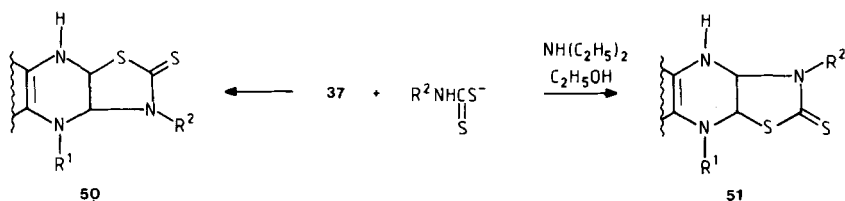


SCHEME 42

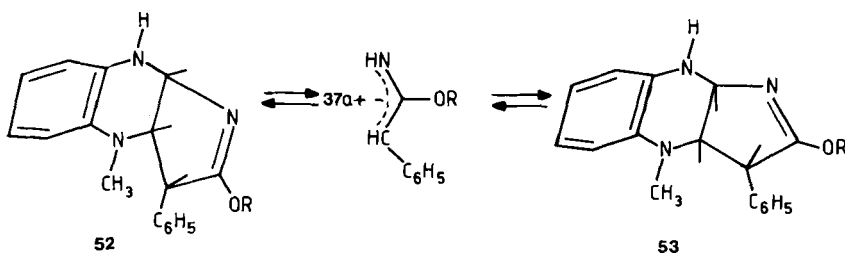
83KGS1120), and imidazo- (83KGS1684; 85KGS390) or thiazoloquinoxalines (84KGS680; 84KGS686; 85KGS1417) have been reported. All these fused heterocyclic systems **46** have been obtained by cyclizations of *N*-alkylquinoxalinium salts with such 1,3-dinucleophiles as β -diketones, thioureas, thioamides, dithiocarbamates, and others (Scheme 41) (84OMR775, 84UK1648; 85KGS1011).

Similarly, heterocyclic systems **47–49**, the tetrahydro analogues of those obtained by reactions of 2,3-dichloroquinoxaline with β -dicarbonyl compounds, thioamides, or dithiocarbamates, have also been prepared (Scheme 42) (84OMR775; 85KGS1011).

An important and characteristic difference between reactions of *N*-alkylquinoxalinium salts with 1,3-dinucleophiles, giving rise to the formation of tetrahydro cycloadducts **46**, and the annelation reactions with 2,3-dichloroquinoxaline is that cycloadduct formation is reversible. Due to the reversibility of the diaddition reactions and the ambident character of the 1,3-dinucleophiles used, regio- and stereoisomeric cyclization products can be formed. Indeed, regioisomeric adducts **50** or **51** can be obtained when quinoxalinium salts **37** react with ammonium dithiocarbamates. It depends on the reaction conditions which product is favored. When the reaction was carried out in aprotic solvents, such as dimethyl sulfoxide (DMSO) or chloroform, only thiazolo[4,5-*b*]quinoxalines **50** could be isolated in good yield. When the same reaction is carried out in an ethanol solution it results in the formation of the regioisomeric thiazoloquinoxalines **51** (Scheme 43) (84KGS680).



SCHEME 43

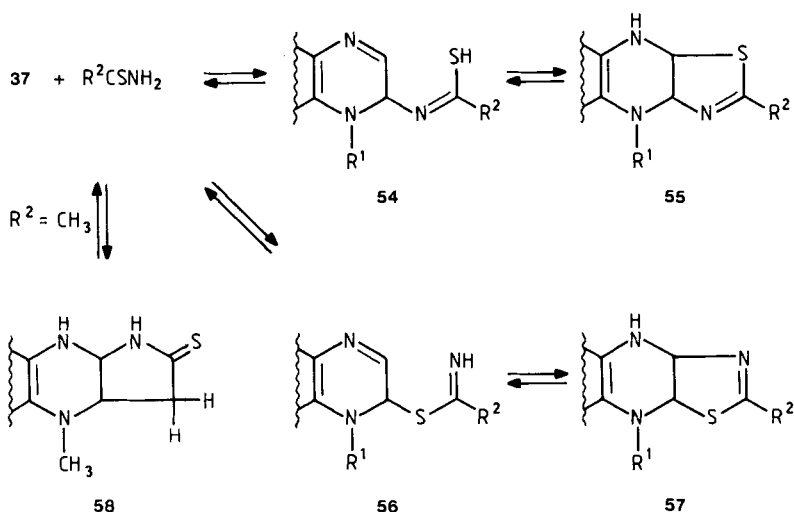


SCHEME 44

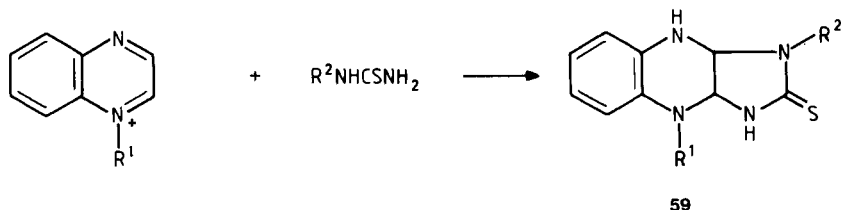
In cyclizations of this type the reaction can be governed by kinetic factors or by conditions favoring the formation of a thermodynamically more stable product. For example, the formation of the kinetically favored pyrrolo[2,3-*b*]quinoxalines **52** with the endo-configuration takes place under basic conditions, while in the absence of a base initially both stereoisomeric adducts **52** and **53** are formed. In the course of the reaction, however, rearrangement of **52** into the thermodynamically more favored exo-adduct **53** occurs (Scheme 44) (81DOK384).

It is interesting to note that, due to the reversible character of the cycloaddition, isomerization favoring the product which is thermodynamically more stable may occur and an appropriate side-chain substituent may participate. For example, the thiazolo[4,5-*b*]quinoxalines **55**, formed in the reaction of quinoxalinium salts with thioamides under kinetically controlled conditions, are able to undergo two different isomerizations (Scheme 45). When compound **55** contains an aryl group at C-2 ($R^2 = \text{aryl}$) and this compound is heated in an ethanolic solution, the thiazoloquinoxaline **57** is formed. In the case of $R^2 = \text{CH}_3$, the methyl group participates in the isomerization process, yielding pyrrolo [2,3-*b*]quinoxalin-2-thione **58** (Scheme 45) (85KGS396).

Since 1,3-bifunctional nucleophiles usually show prototropy (see Section II) several possibilities for annelation to the pyrazine ring exist. In particular, the formation of both thiazolo- and imidazoquinoxalines can be expected in the



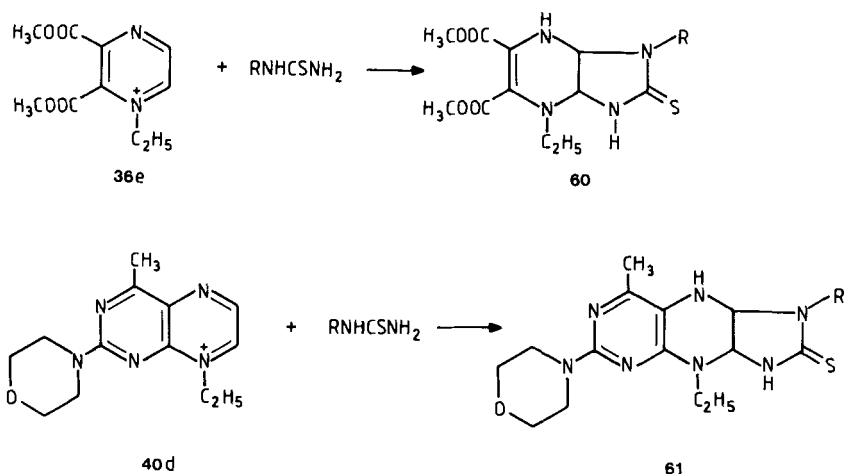
SCHEME 45



SCHEME 46

reaction of quinoxalium salts with thioureas. It has been found, however, that *N*-substituted thioureas act exclusively as *N,N'*-1,3-dinucleophiles yielding the imidazo[4,5-*b*]quinoxalines **59** (Scheme 46) (83KGS1684). It is of interest to mention that, in the disubstitution reactions of thioureas with dichloro-1,4-diazines, the thiourea reacts as an *N,S*-1,3-dinucleophilic reagent, resulting in thiazolo-annelated 1,4-diazines (see Scheme 19) (76JIC1170; 77ZC15; 78IJC(B)683; 80JIC946).

The *N*-ethylpyrazinium **36e** and 8-ethylpteridinium salts **40d** which show, as we have seen (see Tables I and III), some tendency to undergo a diaddition with monofunctional nucleophiles, are also able to react with 1,3-bifunctional nucleophilic reagents to give cyclization products. Thus, reactions of pyrazinium **36e** and pteridinium **40d** salts with thioureas afford



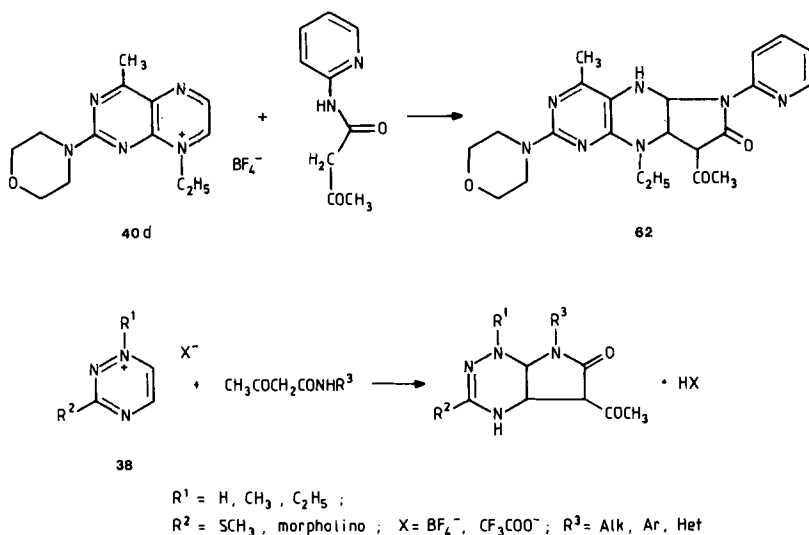
SCHEME 47

the imidazopyrazines **60** and imidazopteridines **61** (Scheme 47) (83KGS1684; 86KGS420).

Qualitative data on the cyclizations of pyrazinium **36**, quinoxalinium **37**, 1,2,4-triazinium **38**, and pteridinium **40** salts with CH-active acetamides show that their reactivities follow the same order as has been established for diaddition reactions with simple nucleophiles (Section III,B,1) (86KGS1380). For example, the anilide of acetoacetic acid readily forms cycloadducts with quinoxalinium salts **37**, but no cyclization products with pteridinium cations **40**. By enhancing the NH-activity of the amide group, the cyclization with pteridinium salts could be achieved. Thus, the *N*-(pyridin-2-yl)-substituted amide of acetoacetic acid is able to undergo the cyclization reaction with the pteridinium cation **40d** to afford pyrrolo[2,3-*g*]pteridine **62** (Scheme 48) (86KGS420).

In a similar manner, NH- and *N*-alkyl-1,2,4-triazinium salts **38** react with acetoacetamides to afford pyrrolo[3,2-*e*][1,2,4]triazines (Scheme 48).

The structures of the tetrahydropyrazines, tetrahydroquinoxalines, and tetrahydropteridines condensed with various five-membered heterocycles, such as furan, pyrrole, imidazole, and thiazole, have been elucidated by ^1H - and ^{13}C -NMR spectroscopy (84OMR775) and X-ray diffraction analyses (81KGS1392; 85KGS1417). The ^1H - and ^{13}C -NMR spectra of these cyclization products proved to be useful for establishing the nature and regio-orientation of the five-membered ring annelated to the pyrazine ring. The values of vicinal couplings between the ring junction protons in the ^1H -NMR spectra of all the compounds studied were found in the range 6–9 Hz



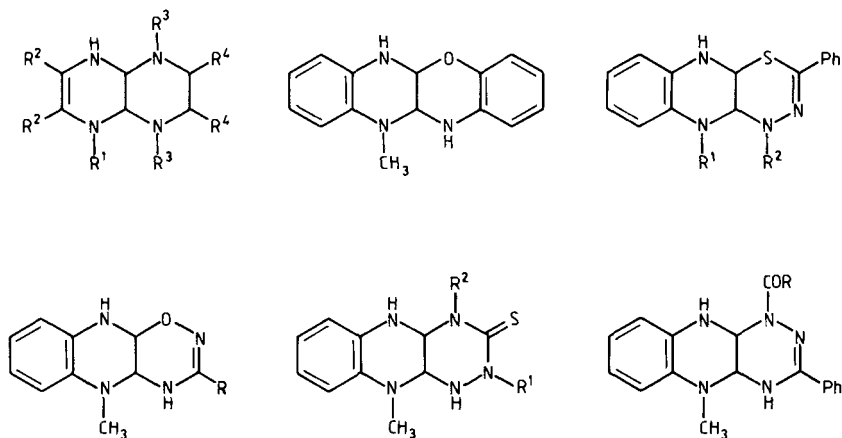
SCHEME 48

(84OMR775), which is characteristic for condensed systems with five-membered ring annelated to the pyrazine ring (84OMR775). These data indicate that there exists a strong similarity in the stereochemistry of the structures. These values were shown to correspond to a *cis* configuration of the ring junction protons. This conclusion was also confirmed by single-crystal X-ray diffractions performed on furo[2,3-*b*]- and thiazolo[4,5-*b*]-quinoxaline derivatives (81KGS1392; 85KGS1417).

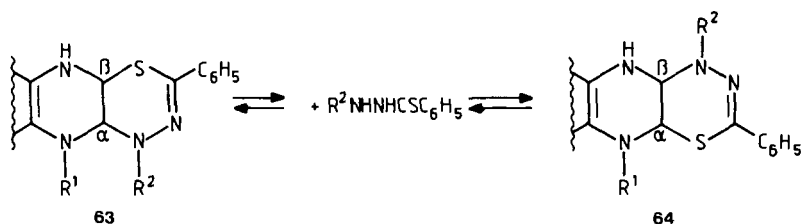
3. Annelation of Six-Membered Heterocycles

Reactions of 1,4-diazinium salts with 1,4-bifunctional nucleophiles are to a great extent similar to those presented in previous sections for the annelation of five-membered heterocycles to the pyrazine ring (84KGS706; 84KGS1284; 85KGS707; 85KGS960; 85KGS1116; 86KGS1011; 86MI1; 87KGS557; 87KGS701).

A number of tetrahydropyrazines and tetrahydroquinoxalines condensed with various six-membered heterocycles, such as pyrazine, oxazine, oxadiazine, thiadiazine, and triazine rings, have been obtained by cyclizations of *N*-alkyl-1,4-diazinium salts with 1,4-bifunctional nucleophiles (Scheme 49) 84KGS706; 84KGS1284; 85KGS707; 85KGS960; 85KGS1011; 85KGS1116; 86MI1; 87KGS557).



SCHEME 49



SCHEME 50

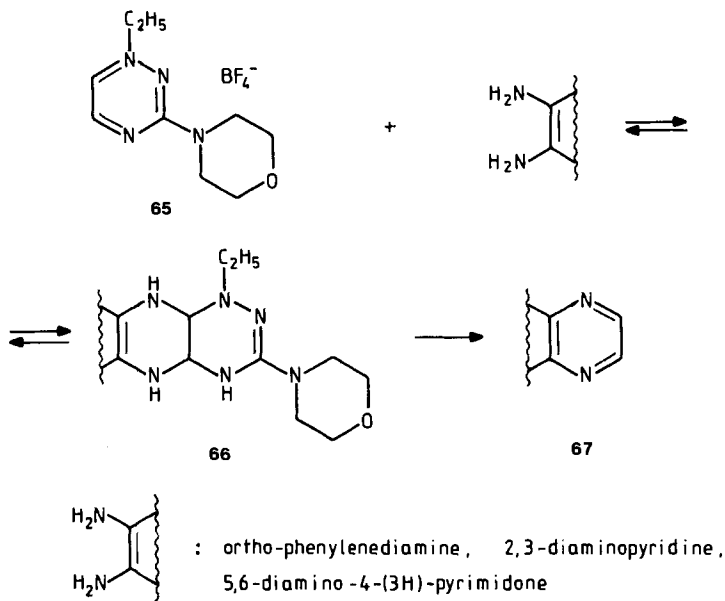
The formation of a mixture of regioisomeric adducts has also been observed in some cases (85KGS1011) and, in particular, in the reaction of quinoxalinium salts with hydrazides of thiobenzoic acid (Scheme 50) (87KGS557, 87KGS701), yielding the thiadiazino isomers **63** and **64**.

The regio-orientation of the annelated 1,3,4-thiadiazine ring in **63** and **64** was established on the basis of the $^1J(\text{CH})$ values for the ring junction carbon resonances in the ^{13}C -NMR spectra (86MI1). Structure **64** ($\text{R}^1 = \text{CH}_3$, $\text{R}^2 = \text{COCH}_3$) was further conclusively proved by X-ray crystallography (87KGS701).

Vicinal couplings $^3J(\text{H-}\alpha, \text{H-}\beta)$ measured in the ^1H -NMR spectra of tetrahydroquinoxalines condensed with six-membered heterocycles proved to be smaller (2–4 Hz) (86MI1) than those found for tetrahydroquinoxalines annelated with five-membered rings (6–9 Hz) (84OMR775). It indicates that tetrahydroquinoxalines annelated to six-membered rings were found to have stereostructures different from those in which the tetrahydropyrazine ring is

annellated to a five-membered heterocycle. The X-ray structure determination of thiadiazino[5,6-*b*]quinoxaline **64** ($R^1 = \text{CH}_3$, $R^2 = \text{COCH}_3$) revealed that the tetrahydropyrazine ring exists in a twisted chair conformation, with the H- α and H- β atoms in pseudoaxial and pseudoequatorial positions (87KGS701). Although the ring junction atoms are still cis-oriented, the torsion angle H(α)-C(α)-C(β) (about 60°) is considerably greater than that in tetrahydroquinoxalines annellated with five-membered heterocycles (19 – 23°), in which the tetrahydropyrazine ring is in a boat conformation (81KGS1392; 85KGS1116; 85KGS1417). The differences in the stereostructure of cycloadducts do explain why ^1H - and ^{13}C -NMR spectral parameters measured for tetrahydroquinoxalines condensed with six-membered heterocycles deviate substantially from the corresponding values for condensed systems in which the tetrahydropyrazine ring is annellated by a five-membered heterocycle. The ^1H - and ^{13}C -chemical shifts for the ring junction proton and carbon resonances as well as the $^1J(\text{CH})$ and $^3J(\text{H-}\alpha, \text{H-}\beta)$ coupling constants were shown to be of diagnostic value for the structural analysis of condensed tetrahydropyrazines and related heterocyclic systems (86MI1).

As already noted, cycloadducts resulting from the diaddition reaction on quaternary 1,4-diazinium salts are able to dissociate to the starting materials. Sometimes the dissociation does not form the starting substrate but instead gives products different from the starting materials. For instance, dissociation

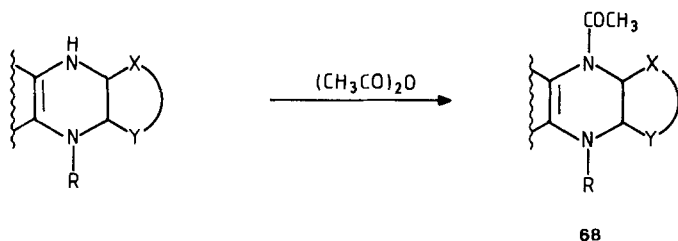


SCHEME 51

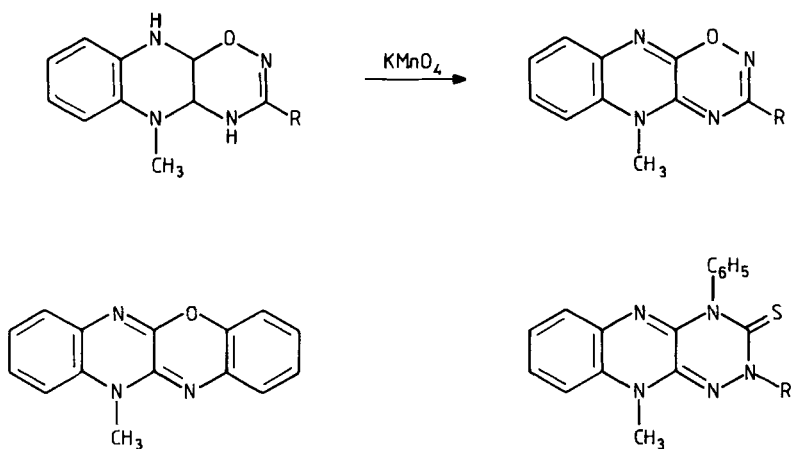
of the cycloadducts **66**, formed from *N*-ethyl-1,2,4-triazinium cation **65** with aromatic 1,2-diamines, do not dissociate into starting material **65** but rather into the pyrazine derivatives **67** (Scheme 51) (87KGS280). This reaction is an interesting but rare example of a ring transformation involving ortho-cyclic adducts as intermediates (87KGS280).

Acylation of the NH group of the tetrahydropyrazine ring (Scheme 52) (81KGS1392; 85KGS396; 85KGS1417) yields the acetyl derivatives **68**, which are found to be stable and not to undergo dissociation even in acidic solution (Scheme 52).

Another way to prevent any dissociation of cyclization products obtained by the diaddition reactions is their conversion into aza-aromatic compounds. Oxidation of cycloadducts by permanganate in acetone yields condensed pyrazine derivatives containing, of course, no ring junction hydrogen atoms. Several examples of condensed systems obtained by this method are shown in Scheme 53.



SCHEME 52



SCHEME 53

Thus, the diaddition reaction of bifunctional nucleophiles to alkyl-1,4-diazinium salts followed by the oxidation of cycloadducts formed provides us with a simple and effective route to preparation of polycyclic aza-aromatic compounds.

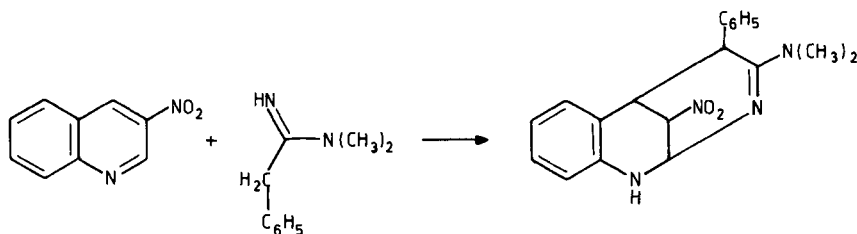
C. META-CYCLIZATIONS AND RING TRANSFORMATION REACTIONS

The specific features of meta-cyclization of aza-aromatic compounds with bifunctional nucleophilic reagents were formulated by Strauss in a number of papers on the reactions of polynitro aromatics and their aza-analogues with enamines, CH-active acetamidines, and other 1,3-dinucleophiles (74ACR181).

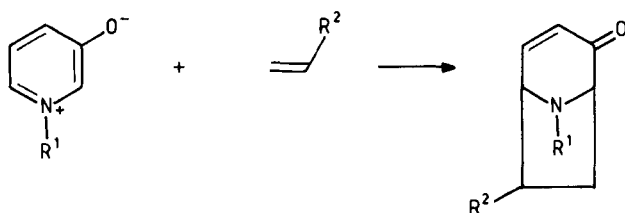
Meta-cyclizations are often called meta-bridging reactions, since they yield polycyclic meta-bridged structures (74ACR181). In the series of aza-aromatic compounds, these reactions are mostly found with 3-nitro-substituted azines or with 1,3-diazines, as illustrated by Scheme 54 (77JOC2589).

The meta-bridging cyclizations of azines with bifunctional nucleophiles usually occur in two steps and differ substantially in that respect from the 1,3-dipolar addition reactions performed on 3-hydroxypyridinium salts, which also result in meta-bridged adducts (Scheme 55) (76JCS(P1)2285).

Meta-bridged adducts of aza-aromatic compounds appear to be less stable than their nitro analogues or ortho-annulated azine derivatives (74ACR181;

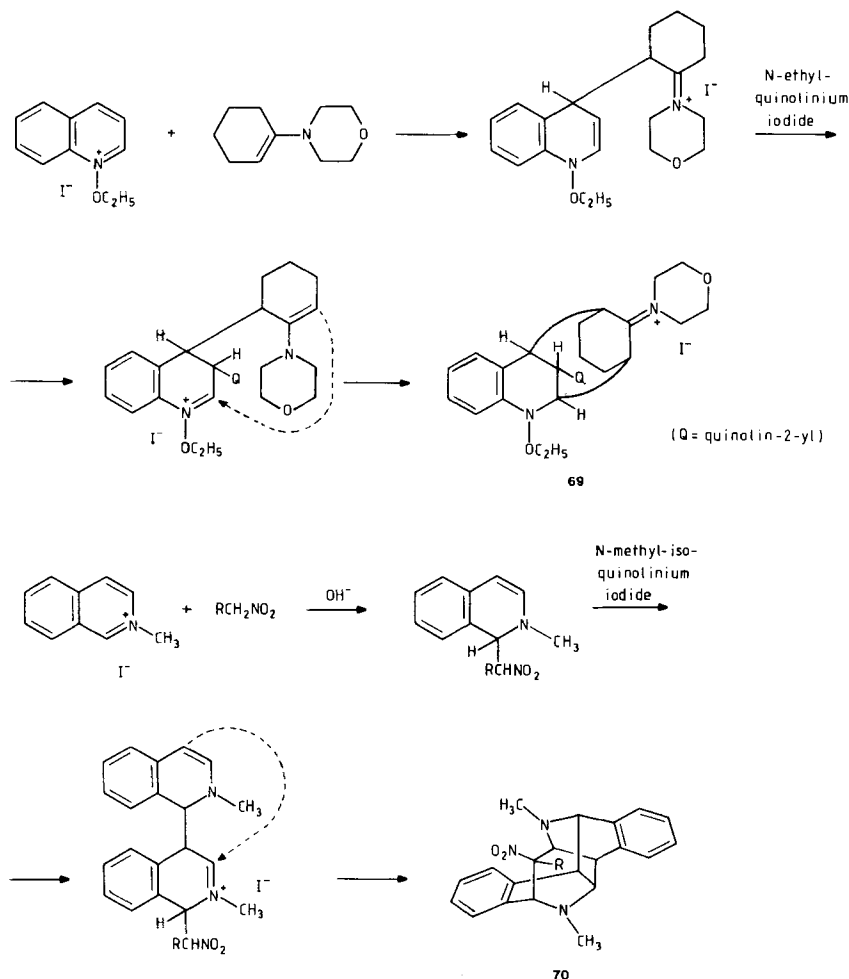


SCHEME 54

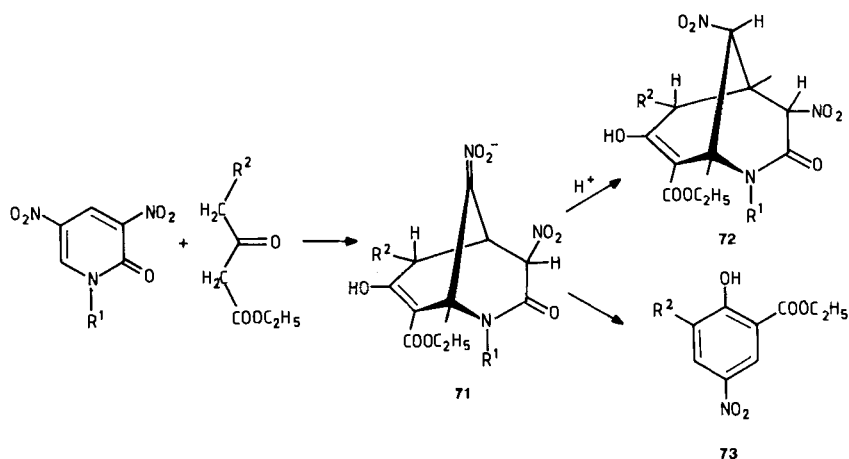


SCHEME 55

84UK1648). Meta-bridged azine adducts are difficult to isolate and their ^1H -NMR spectra are difficult to obtain because the adducts are not stable and are readily converted into other cyclic systems. In some cases their formation is accompanied by various side reactions. For example, meta-cyclization of *N*-ethoxyquinolinium iodide with enamines is possible due to the addition of the second molecule of the quinolinium cation to C-3 of the 1,4-dihydroquinoline intermediate, regenerating the $\text{C}_2=\text{N}^+$ iminium fragment, followed by the intramolecular cyclization into complex polycyclic derivatives **69** (Scheme 56) (75CPB2918; 75H1127). In a similar way, the meta-bridged isoquinoline



SCHEME 56



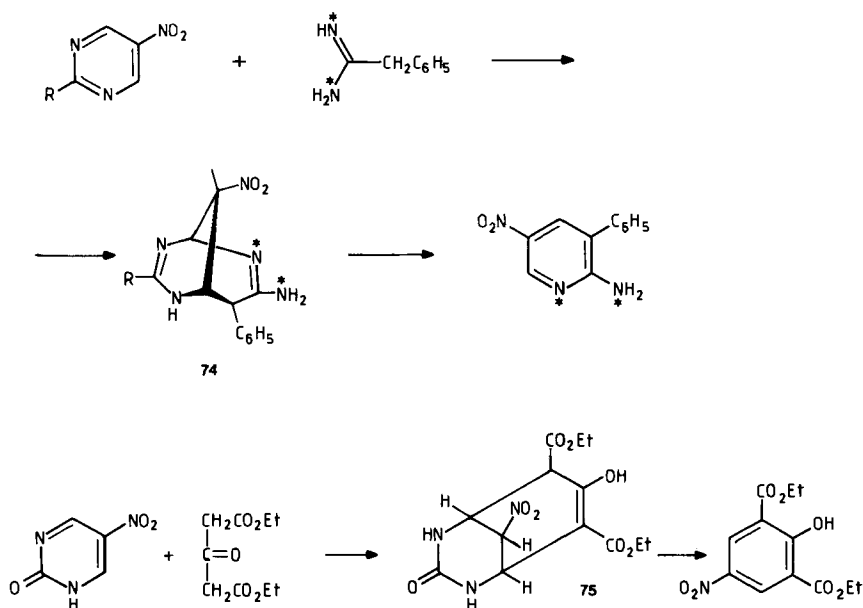
SCHEME 57

derivatives **70** are formed when *N*-methylisoquinolinium iodide reacts with nitroalkanes in the presence of a base (Scheme 56) (69TL1405; 72JHC675). In this multistep cyclization, nitroalkanes behave as 1,1-bifunctional nucleophilic reagents.

The most intriguing chemical behavior of bicyclic meta adducts is their potential to arrange into monocyclic systems. For example, the sodium salt of β-dicarbonyl compounds has been shown to transform 3,5-dinitropyridin-2-ones into nitrophenols **73**. This ring-transformation reaction seems to occur via the bicyclic intermediate **71**, since the latter can be isolated as neutral bicyclic compounds **72** on acidification of the reaction mixture (Scheme 57) (79BCJ2413; 79TL1393; 82BCJ2174; 85BCJ393).

Diazines and triazines can also undergo ring transformation with amidines and related 1,3-*N,N*-dinucleophilic reagents; 1,3-bridging explains the formation of the products. For example, in the conversion of 2-*R*-5-nitropyrimidine into the 2-aminopyridine derivative (Scheme 58) by action of carbanions of ketones or α-phenylacetamide (78RTC256; 82JOC1077), meta-bridged adducts **74** are supposed to be intermediates; they are, however, not isolated. Experimental data using the [¹⁵N]-1,3-*N,N*-dinucleophilic phenylacetamide, coupled with the fact that the cycloadduct **74** (R = SCH₃) resulting from the reaction of 2-methylthio-5-nitropyrimidine with α-phenylacetamide has been detected by ¹H-NMR spectroscopy, suggests the possibility of such a 1,3-bridging mechanism (Scheme 58) (83JOC2667).

The transformation of 5-nitropyrimidin-2-ones into nitrophenols by β-dicarbonyl compounds has also been shown to proceed via the bicyclic meta-bridged intermediates **75** (Scheme 58) (82JOC1081).

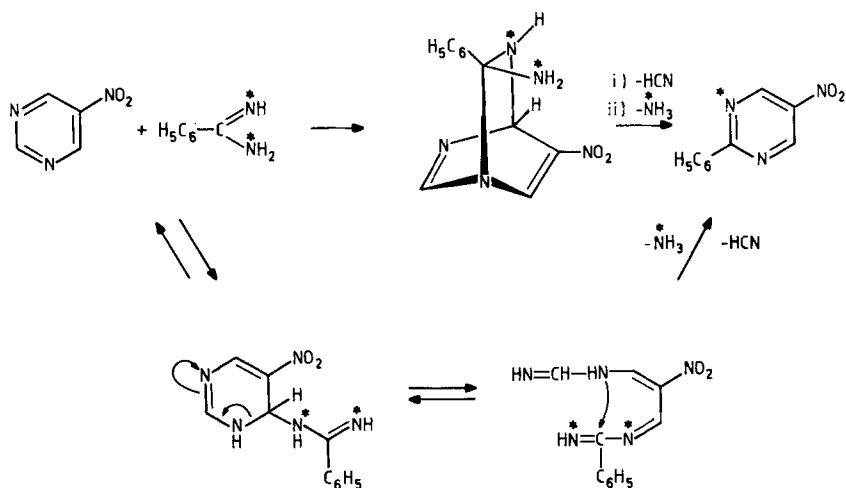


SCHEME 58

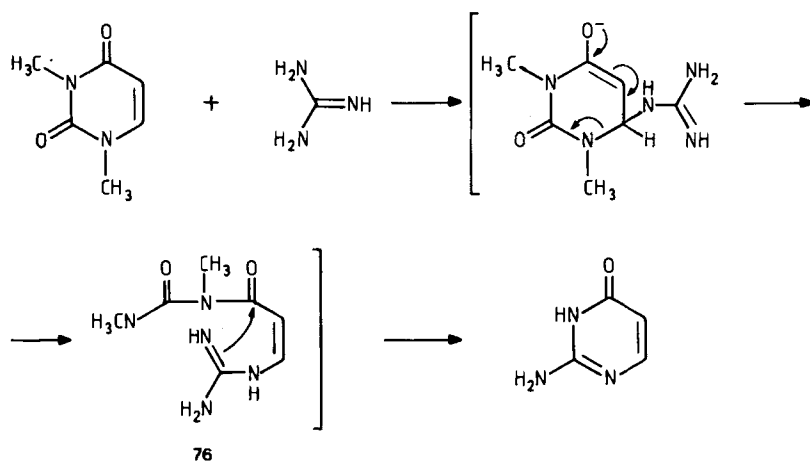
One has to be aware that in cases where the meta-bridged bicyclic intermediates cannot be isolated, alternative routes to product formation can be proposed: (1) the ANRORC mechanism (addition of the nucleophile, ring opening and ring closure) or (2) cycloaddition. An example to illustrate these possibilities is the ring conversion of 5-nitropyrimidine into 2-phenyl-5-nitropyrimidine by benzamidine (82JOC1077; 86JOC71). In this reaction, no meta-bridged nitro intermediate was isolated and, based on ¹⁵N-labeling studies, it was concluded that in this conversion an open-chain intermediate as well as a para cycloadduct are involved (see also Section III,D) (Scheme 59).

An interesting series of ANRORC-type reactions have been described in which the N-1—C(O)—N-3 part of a uracil derivative is replaced by the N—C—N part of 1,3-dinucleophilic reagent (Scheme 60). The transformations are supposed to involve an open-chain intermediate like 76 as the most plausible one (Scheme 60) (77JHC537; 78JOC1193; 79JA4423; 79JOC3982; 80H407; 81CPB3760; 81JOC846; 81TL2409; 82T1405; 83JCS(P1)1293; 83JHC457; 84H289; 84JCS(P1)1859; 84JHC1543; 85JOC1512).

From the above-mentioned examples it is evident that the question whether in this type of transformation bicyclic meta-bridged adducts are key intermediates or not is still under discussion and unsolved. Data published



SCHEME 59



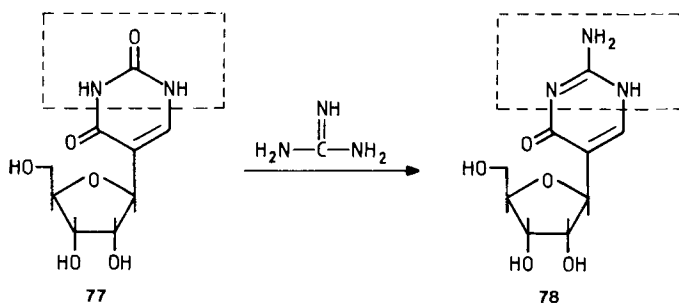
SCHEME 60

so far show that the formation of such cycloadducts in the course of ring transformation reactions is quite possible (79TL1393; 82JOC1081; 83JOC2667; 84H289; 84UK1648).

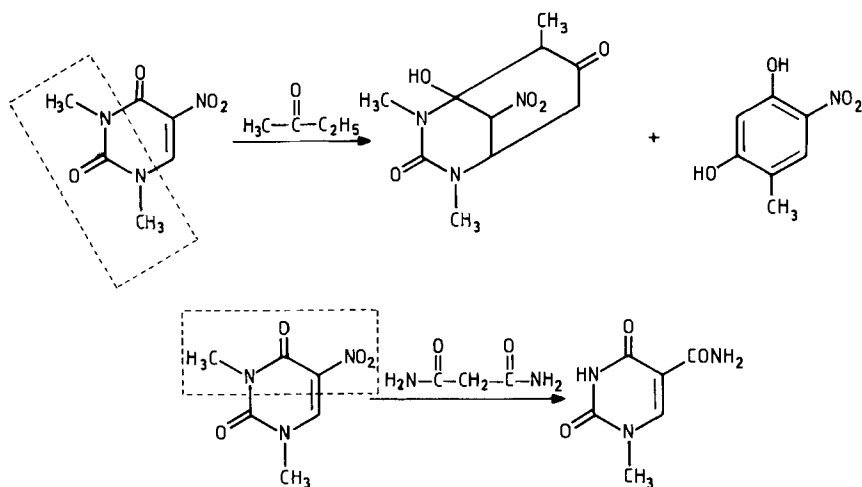
The mechanisms of these ring transformation reactions attract the attention of many synthetic chemists, since they provide simple routes to prepare useful heterocyclic compounds. Interesting examples are those in

which, by action of bifunctional nucleophiles, a pyrimidine ring is converted into another functionalized pyrimidine ring. We can mention the synthesis of a number of pyrimidine nucleosides of biological interest (84H289). Thus, pseudouridine **77** was converted into pseudoisocytidine by action of guanine (Scheme 61) (77JHC537; 78JOC1193).

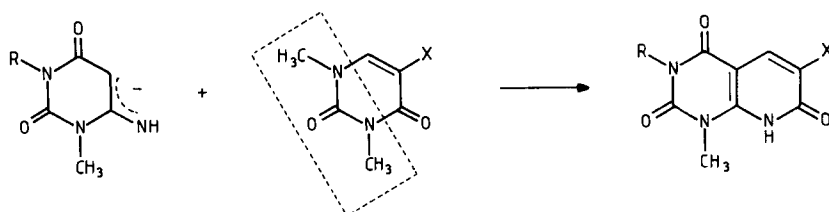
A number of other transformations of uracils are known in which the C—N, C—C—N, or N—C—N moiety of the pyrimidine ring is replaced by various fragments of bifunctional nucleophiles (82T1405; 83JHC457; 84H289; 84JCS(P1)1859; 84JHC1543; 84UK1648). Two examples are shown in Scheme 62.



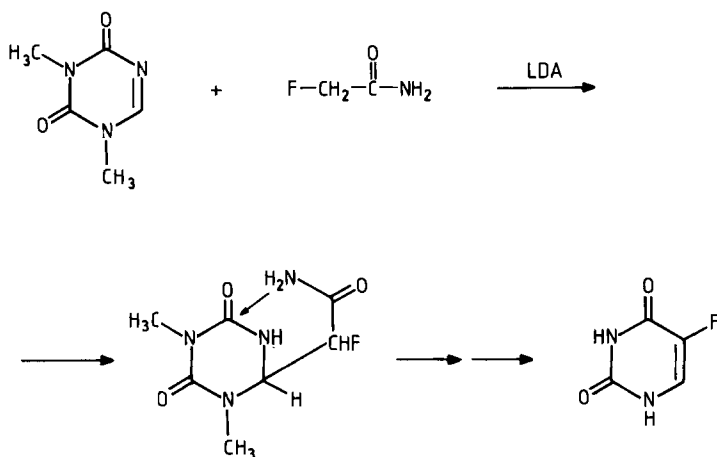
SCHEME 61



SCHEME 62



SCHEME 63

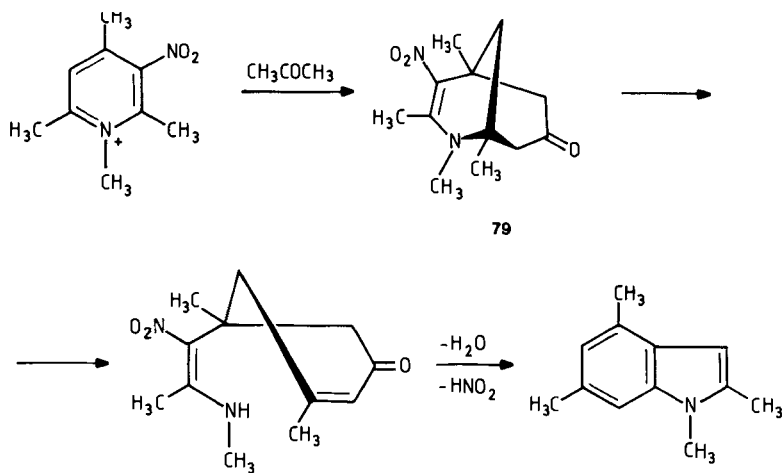


SCHEME 64

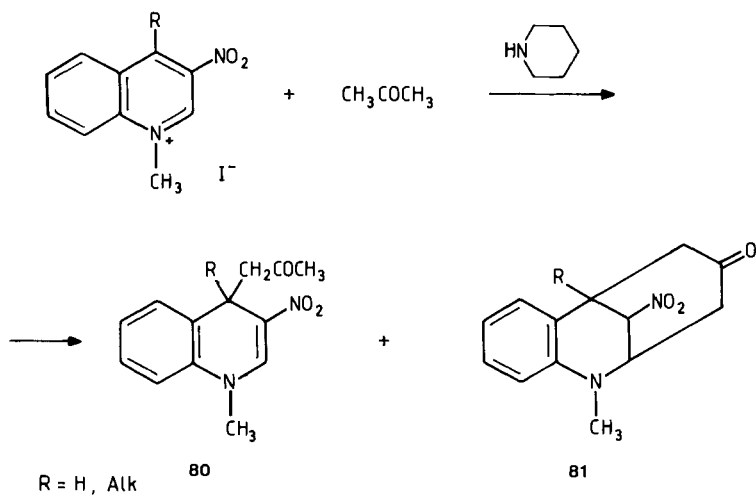
Also the synthesis of pyrido[2,3-*d*]pyrimidines has been achieved by replacement of the N—C—N fragment of 1,3-dimethyluracil with the C,C,N-binucleophilic part of a 6-aminouracil derivative (Scheme 63) (80H407; 81JOC846).

Another ring transformation reaction that may involve either a cycloadduct and/or open-chain intermediate is the synthesis of the antitumor 5-fluorouracil from a triazine by action of fluoroacetamide (Scheme 64) (83JHC457; 84H289).

The transformations of 3-nitropyridinium salts into indole derivatives by the action of ketonic carbanions seem to be a very promising and useful method for the preparation of indoles (Scheme 65) (85KGS509; 85KGS522). The mechanism of this reaction is not quite clear, but bicyclic meta-bridged adducts **79** may be intermediates (Scheme 65).



SCHEME 65



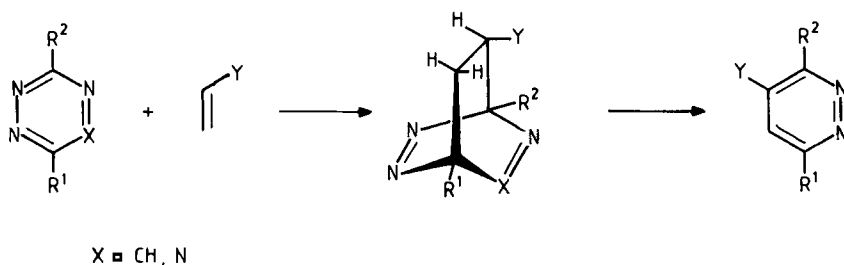
SCHEME 66

A similar reaction of 3-nitroquinolinium salts with ketones in the presence of piperidine results in the meta-bridged cycloadducts **81** together with the C-4 addition product **80** (Scheme 66). Since the meta-bridged adducts **81** are more stable than their pyridine analogues (**79**), they do not react further.

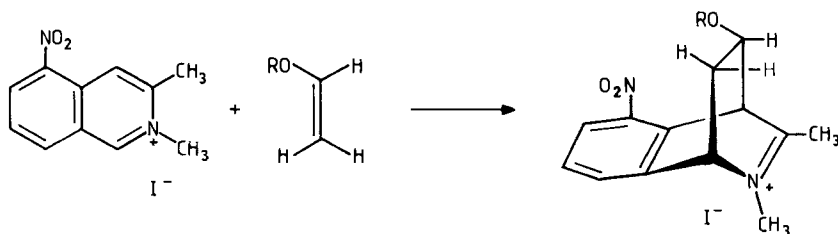
D. PARA-CYCLIZATIONS

The Diels–Alder reaction with inverse electron demand, in which a 4- π electron fragment of an aza-aromatic acts as a diene and nucleophilic reagent with electron-enriched double bond as a dienophile, appears to be the most widely used method for the formation of para-bridged bicyclic systems (74PAC569; 80AG773; 83T2869; 86CRV781). In accordance with the frontier molecular orbital (FMO) theory, cyclizations of this type are favored when the azine molecule contains strong electron-withdrawing groups or a cationic center, lowering the lowest unoccupied molecular orbital (LUMO) energies quite considerably (74PAC569; 76MI1; 80AG773). That is why 1,2,4,5-tetrazines, 1,2,4-triazines, and 5-nitropyrimidines have a great tendency to undergo $[4 + 2]$ -cycloaddition reactions (Scheme 67) (80AG773; 81KGS1462; 82TL3965; 83T2869; 85CZ348; 85H683; 85TL2415; 85TL4355; 86AP798; 86CRV781).

The cycloaddition reaction on the azadiene substrate is usually followed by elimination of nitrogen, hydrogen cyanide, water, amines, or other simple compounds and, as a result of this retrograde process, a new carbo- or heterocyclic system is formed (Scheme 67). The method provides a very convenient route to the synthesis of many not easily accessible compounds. In



SCHEME 67



SCHEME 68

particular, an elegant synthesis of 4-nitro- and 4-cyanopyridazines by means of the cycloaddition of 1,2,4,5-tetrazines with nitro- and cyanoenamines has been developed (Scheme 67, $X = N$; $Y = CN, NO_2$) (85H683).

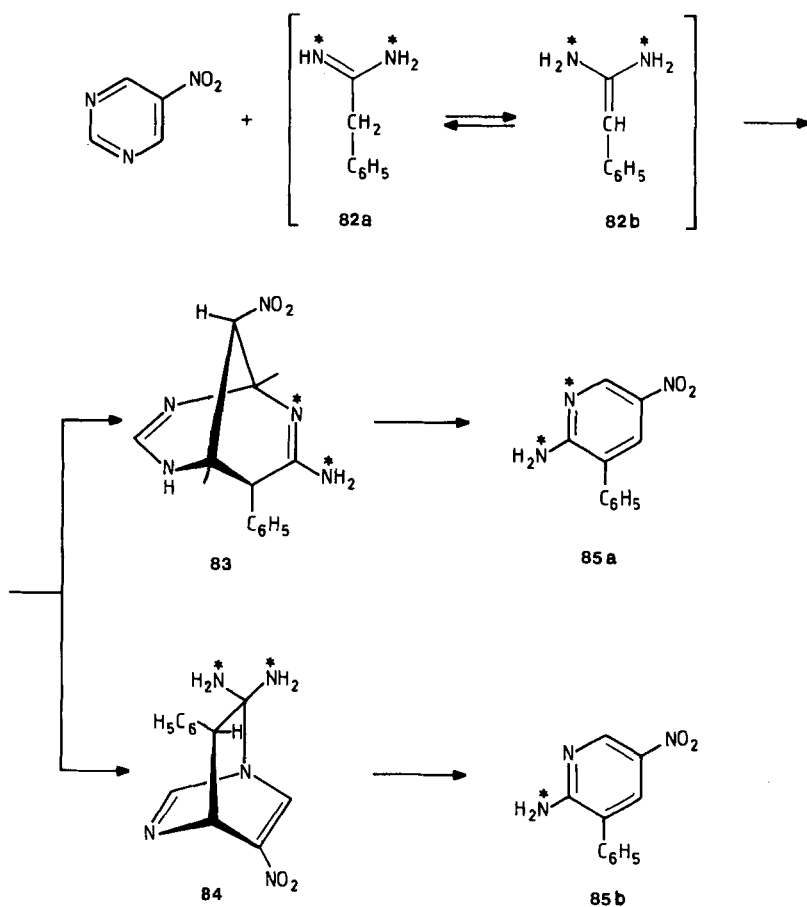
Isoquinolinium and acridizinium cations also readily participate in the cationic $[4 + 2]$ -cycloaddition reactions (Scheme 68) (697OC1700; 71TL409; 72KGS579; 73AG(E)212; 73CC156; 73JHC1031; 74AHC289; 74JHC23; 75JOC1195; 79JOC27; 79JOC4680).

A great variety of 1,3-bifunctional nucleophiles contain in their structure an electron-enriched double bond and, therefore, are able to react as dienophiles with azadienes in a Diels–Alder-type reaction. There are indeed reactions known in which 1,3-ambident reagents act both as dienophiles and 1,3-dinucleophiles (see discussion in Section III,C). Thus, investigation into the mechanism of the degenerate ring transformation of 5-nitropyrimidine into 2-substituted 5-nitropyrimidines by action of $[^{15}N]$ amidines has revealed that there are at least two mechanistic pathways operating in this ring-transformation reaction which lead to incorporation of either the $N-C-N$ or the $C-N$ fragments of the amidine (86JOC71). An increase in electron-donating character of the substituent R in the electron-rich amidine $R-C(=NH)NH_2$ has been found to result in a greater percentage of $C-N$ incorporation into the pyrimidine ring. From these data it is clear that the $C-N$ incorporation of the amidine into the pyrimidine ring certainly occurs according to a mechanism in which not only an open-chain compound but also a para-cycloadduct is involved (Scheme 59) (86JOC71).

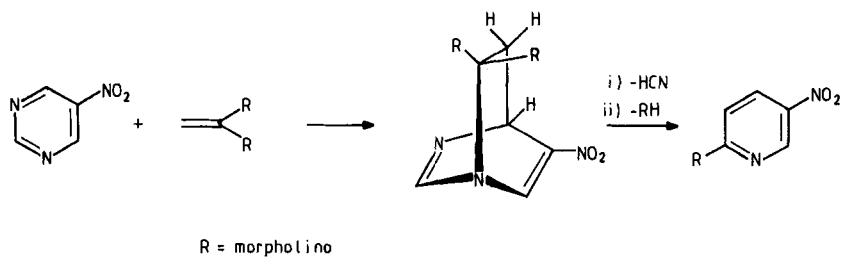
Also, it has been shown by ^{15}N -labeling experiments that transformations of 5-nitropyrimidines into pyridine derivatives by the action of α -phenylacetamidines could proceed via different pathways involving the formation of open-chain intermediates, meta-bridged cycloadducts **83**, as well as para-bridged intermediates **84** (Scheme 69) (82TL3965; 83JOC2667). In the latter case, α -phenylacetamide acts as the enediamine **82b**, causing the $C-C$ fragment to be included into the pyridine ring **85b**. Experimental support for the formation of the para-bridged intermediate **84** is also provided by the fact that 5-nitropyrimidine participates in a Diels–Alder reaction with 1,1-dimorpholinoethene (the structural analogue of the enediamine **82b**) to yield 2-morpholino-5-nitropyridine via the corresponding para-bridged cycloadduct (Scheme 70) (82TL3965; 83JOC2667).

Theoretical analysis of this $[4\pi + 2\pi]$ -cycloaddition reaction by consideration of frontier-orbital interactions between the electron-rich olefin (highest occupied molecular orbital, HOMO) and the electron-poor 5-nitropyrimidine (LUMO) has shown that the FMO perturbation theory correctly predicts an exclusive regiospecific addition of the enamine to N-1 and C-4 of the pyrimidine ring (86JOC4070).

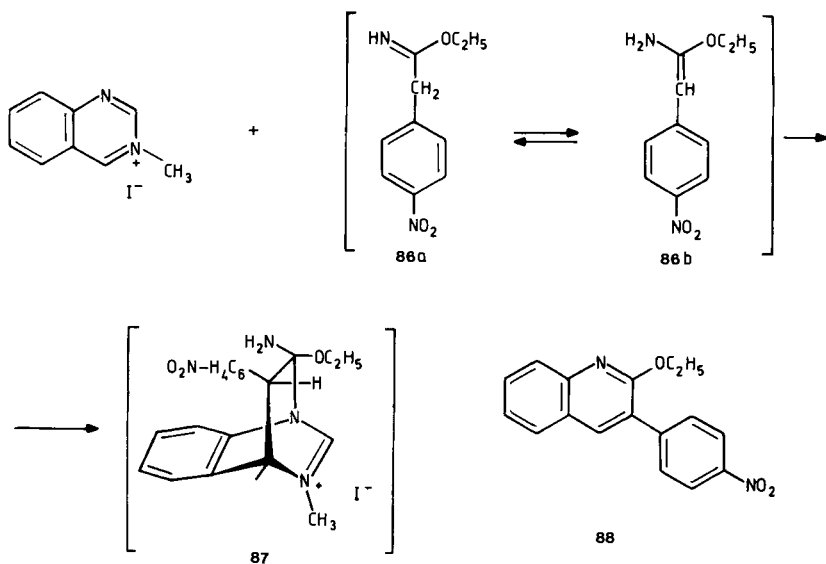
The transformation of quinazolinium salts into quinoline derivatives **88** by



SCHEME 69



SCHEME 70

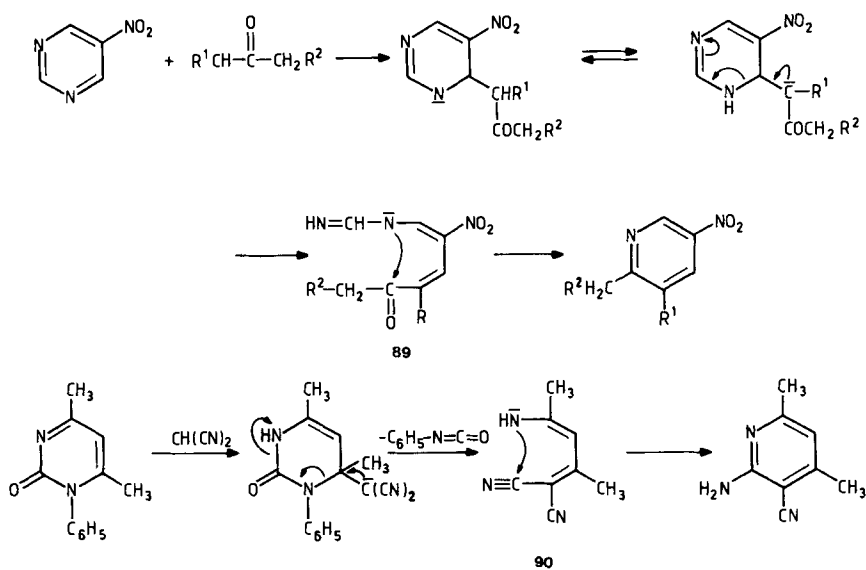


SCHEME 71

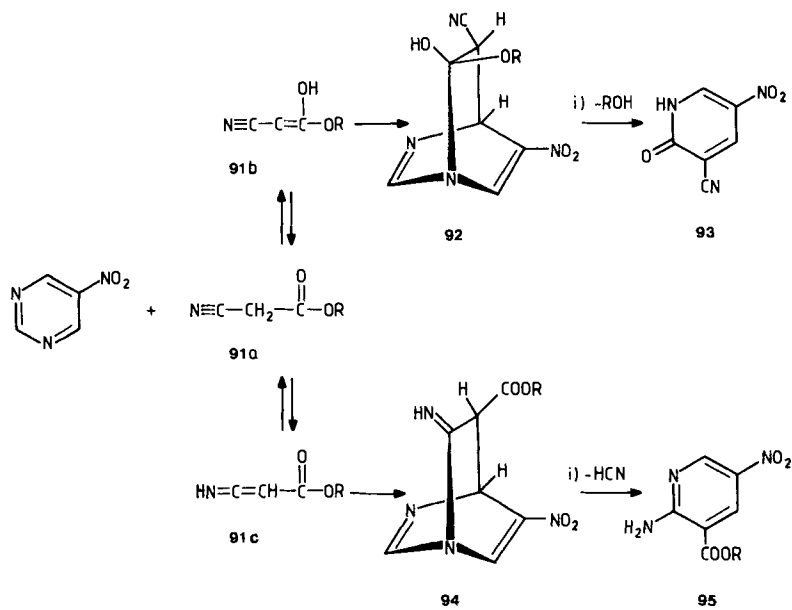
action of ethyl *p*-nitrophenylacetimidate (**86**) has been rationalized via the intermediacy of the para-bridged cycloadduct **87** (Scheme 71) (81KGS1549).

A great number of papers describe ring transformations in which the N-1—C-2 portion of the pyrimidine ring is replaced by a C—C fragment of acetone, acetylacetone, aceto- and cyano-acetic acid esters, malononitrile, and other active methylene compounds (73JCS(P1)1615; 73JCS(P1)1620; 73JCS(P1)1794; 73JCS(P1)1974; 74RTC233; 78RTC256; 80JHC413; 83RTC373; 84CPB2942).

It is common practice to classify these pyrimidine-to-pyridine transformations as recyclization reactions proceeding via open-chain intermediates like **89** and **90** (Scheme 72) (78RTC256; 84CPB2942). One cannot, however, exclude the possibility that this type of ring-modifying reaction occurs via $[4\pi + 2\pi]$ -cycloaddition on the N-3,C-6-positions of the pyrimidine ring, provided active methylene compounds are able to form a tautomeric form with the C=C bond. This mechanism has been advanced, in particular, for the conversion of 5-nitropyrimidine into pyridine derivatives **93** and **95** by action of active methylene compounds **91** (Scheme 73) (83RTC373). Cyanoacetic acid esters **91a** may react as enols **91b** or tautomeric imino compounds **91c**. The participation of these two forms in the $[4\pi + 2\pi]$ -cycloaddition reaction on the pyrimidine ring give rise to cycloadducts **92** and **94**, followed by the retrograde process yielding pyridines **93** and **95**, respectively (Scheme 73) (83RTC373).



SCHEME 72



SCHEME 73

IV. Conclusion

Reactions of azines with bifunctional nucleophiles can give rise to several cycloadducts, the structure depending on the nature of reagents, the structure of the azine substrate, and the reaction conditions. As discussed above, three types of cycloadducts are proposed to be formed in reactions of azines with such 1,3-N,C-dinucleophiles as acetamidines and acetimino esters (Schemes 44, 54, 58, 69, and 71).

Ortho-cyclization products can usually be isolated, while meta- and para-bridged cycloadducts are unstable and are often transformed into other heterocyclic systems. Their presence as intermediates can, however, often be rationalized by spectroscopic methods or ^{15}N -labeling studies.

Many of the reactions discussed provide a very convenient synthetic route to a great variety of azine derivatives. It seems to be a very interesting and promising area of heterocyclic chemistry and there is no doubt that further investigations into this field will allow new syntheses of useful compounds to be developed.

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